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ORIGINAL SUBMISSION

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Soymilk, Beverages, Tofu, Oriental Pasta, and Specialty Items

December 30, 1998

Dr. Linda Kahl  
Office of Pre-Market Approval  
FOOD & DRUG ADMINISTRATION  
200 C Street SW, HFS - 206  
Washington DC 20204  
Office (202) 418-3101 Fax (202) 418-3131

Dear Dr. Kahl:

Thank you for your call this morning. Enclosed are two additional copies of the "Safety Assessment of Nine Herbal Ingredients" document for food safety review. The materials were prepared by Professor P.P.H. But, Department of the Chinese Medicinal Material Research Center of the Chinese University of Hong Kong. We would like your office to review the ingredient safety information provided, and let us know whether they can be used in herbal tea beverage application. Please contact me at our San Francisco manufacturing location: 1575 Burke Avenue, San Francisco CA 94124, Phone (415) 285-1130 X203 or fax (415) 285-0327.

Vitasoy USA Inc. is planning to introduce one or two herbal tea beverages that will contain all or some of the nine herb mentioned below. The tea beverage will be packaged in a single serve aseptic 250 mL Tetra Pak carton, and will be imported from Hong Kong for US and Canada. The target market is North America Chinese American market, and it is suitable for child and adult consumptions.

The nine herbal ingredients are:

*Dendranthema morifolium* (Chrysanthemum)

*Morus alba* (Mulberry Leaf)

*Glycyrrhiza uralensis* (Licorice)

*Plumeria rubra*

*Lonicera japonica* (Honey Suckle)

*Prunella vulgaris* (Self Heal)

*Lophatherum gracile*

*Sophora japonica* (Pagoda Tree Blossom)

*Mesona chinensis* (Jellywort)

Sincerely,

Janet M. Pang  
R&D Manager  
Enclosure

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AZUMAYA • NASOYA • NEW MENU • VITA • VITASOY • 維他奶 • 維他山

Vitasoy (U.S.A.) Inc. HDQ • 400 Oyster Point Blvd. Suite 201, South San Francisco, CA 94080 Phone (415) 583-9888 (800) VITASOY Fax (415) 583-8881

Manufacturing • 1575 Burke Avenue, San Francisco, CA 94124 Phone (415) 285-1130 Fax (415) 285-0327

EX 203



Soymilk, Beverages, Tofu, Oriental Pasta, and Specialty Items

December 15, 1998

Dr. Alan Rulis  
Office Director of Pre-Market Approval Department  
FOOD & DRUG ADMINISTRATION  
200 C Street SW, 8FS - 200  
Washington DC 20204  
Office (202) 418-3100 Fax (202) 418-3131

Dear Dr. Rulis:

I am submitting the enclosed "Safety Assessment of Nine Herbal Ingredients" document for food safety review. The materials were prepared by Professor P.P.H. But, Department of the Chinese Medicinal Material Research Center of the Chinese University of Hong Kong. We would like your office to review the ingredient safety information provided, and let us know whether they can be used in herbal tea beverage application.

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The nine herbal ingredients are:

<i>Dendranthema morifolium</i> (Chrysanthemum)	<i>Morus alba</i> (Mulberry Leaf)
<i>Glycyrrhiza uralensis</i> (Licorice)	<i>Plumeria rubra</i>
<i>Lonicera japonica</i> (Honey Suckle)	<i>Prunella vulgaris</i> (Self Heal)
<i>Lophatherum gracile</i>	<i>Sophora japonica</i> (Pagoda Tree Blossom)
<i>Mesona chinensis</i> (Jellywort)	

Sincerely,

Janet M. Pang  
R&D Manager  
Enclosure

cc: (Letter only) Joe Ho, Sue Lau, Yvonne Lo, Angela Ip, Jacqueline Chu

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Vitasoy (U.S.A.) Inc. HDQ • 400 Oyster Point Blvd. Suite 201, South San Francisco, CA 94080 Phone (415) 583-9888 (800) VITASOY Fax (415) 583-8881

Manufacturing • 1575 Burke Avenue, San Francisco, CA 94124 Phone (415) 285-1130 Fax (415) 285-0327

**From the Desk of Prof. P.P.H. But**  
**c/o Laboratory for the Chemical Quality Control of**  
**Chinese Medicines and Health Foods**

Address: Chinese Medicinal Material Research Centre, The Chinese University of Hong Kong, Shatin N.T., Hong Kong.  
Tel: (852) 2609-6140 Fax: (852) 2603-5248

**Safety Assessment of Vita Herbal Tea Drink**

1. The Vita Herbal Tea Drink, presented in 250 mL tetrapack, is a sweetened beverage intended for use by people of all ages.
2. The formulation for the production of a liter of this Drink is as follows:

a) <i>Dendranthema morifolium</i> 菊花	< 2 g
b) <i>Glycyrrhiza uralensis</i> 甘草	< 2 g
c) <i>Lonicera japonica</i> 金銀花 △	< 2.5 g
d) <i>Lophatherum gracile</i> 淡竹葉 ○△	< 2 g
e) <i>Mesona chinensis</i> 涼粉草	< 12 g
f) <i>Morus alba</i> 桑葉 ○△	< 1 g
g) <i>Plumeria rubra</i> 雞蛋花 △	< 2 g
h) <i>Prunella vulgaris</i> 夏枯草 ○	< 2 g
i) <i>Sophora japonica</i> 槐花米 △	< 2.5 g
j) honey	< 2 g
k) caramel	< 2 g
l) sodium citrate	< 0.5 g
3. For this safety assessment of the Vita Herbal Tea Drink, search for scientific publications on each of the nine herbs (a-i above) and on herbal teas containing all or some of these nine herbs was conducted on the following computer databases:
  - (a) Medline of the US National Library of Medicine,
  - (b) TCM Database of the Chinese Medicinal Material Research Centre, the Chinese University of Hong Kong; and
  - (c) CHIMERA, a database on cases of adverse reactions due to Chinese medicines developed by the Chinese Medicinal Material Research Centre, the Chinese University of Hong Kong.
4. The results of our database search for each of the nine herbs are presented in the attached report. The herbs are indeed very commonly used in the preparation of herbal drinks. No serious side effect is known, except that a few cases of allergic reactions have been reported for oral consumption of products containing *Glycyrrhiza uralensis* (licorice, an item generally regarded as safe) or *Prunella vulgaris* (selfheal). Such allergic reactions are, however, rare.

5. General practice in home-made herbal teas prepared from these herbs would use about 100 g of the herbs, boil in about 3 L of water for an hour, and produce 2 L of a herbal tea. The concentration of such teas is about 0.05 g herb equivalent per mL of the final herbal drink. There is no absolute dosage range, but generally the daily intake is about 300-500 mL per adult or about 200-300 mL per child. No report on adverse reactions to such herbal teas is known in scientific literature. A pessimistic estimate is the possibility of allergic reactions that may happen in rare occasions, or even that such teas may better be avoided by pregnant women in poor health conditions.
6. On the basis of the formulation as stated by the manufacturer, the concentration of the Vita Herbal Tea Drink is no more than 0.028 g herb equivalent per mL, or half of the normal concentration of home-made herbal teas. In other words, intake of about 2-4 tetrapacks by adults or 1-2 tetrapacks by children in a single day of the Vita Herbal Tea Drink would amount to the general daily intake of home-made herbal teas.
7. Since the nine herbs and the herbal drinks prepared from these herbs are only known to cause minor adverse reactions, such as rare cases of allergic responses, and the concentration of the Vita Herbal Tea Drink is no more than half of that of home-made herbal teas, the Vita Herbal Tea Drink is considered safe for general consumption.

Authorized Signature:

Date: October 26, 1998

## CONDITIONS OF ISSUE OF SAFETY ASSESSMENT REPORT

1. This Safety Assessment Report (SAR) is confidential to the Applicant (Vitasoy International Holdings Ltd.) to whom it is issued and it will be strictly treated as such by Laboratory for the Chemical Quality Control of Chinese Medicines and Health Foods (LCQCCMHF) at the Chinese Medicinal Material Research Centre (CMMRC), The Chinese University of Hong Kong (CUHK). This SAR may not be reproduced either in its entirety or in part and it may not be used for advertising. The Applicant to whom the Report is issued may, however, show or send it, or a certified copy thereof prepared by LCQCCMHF, to his customer, supplier or other people directly concerned. LCQCCMHF will not, without the consent of the Applicant, enter into any discussion or correspondence with any third party concerning the contents of this SAR.
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**Safety assessment of**  
**Herbs used by**  
**Vitasoy International Holdings Ltd.**  
**for producing a herbal drink**

**Mr. Joe Ho** (Technical Director)  
Vitasoy International Holdings Ltd., 1, Kin Wong Street, Tuen Mun,  
New Territories, Hong Kong.  
26 October 1998

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## I. GRAS EXEMPTION CLAIM

### A. Name and Address of Notifier :

Mr. Joe Ho (Technical Director)  
Vitasoy International Holdings Ltd., 1, Kin Wong Street, Tuen Mun, New Territories, Hong Kong.

### B. Name of Substance :

1. **Chrysanthemum** is commonly known as Juhua 菊花 in Chinese.

#### 2. Description

This herb comes from the flower heads (capitulum, a special type of inflorescence frequently misnamed as 'flowers') of *Dendranthema morifolium* (Ramat.) Tzvel. (Compositae), commonly known as Chrysanthemum or Juhua 菊花 in Chinese (Hsu et al., 1986; Anonymous, 1995).

#### 2.1. Botanical

##### 2.1.1. Botanical name

*Dendranthema morifolium* (Ramat.) Tzvel., also known as *Chrysanthemum morifolium* Ramat. or *Chrysanthemum* × *grandiflorum* of Compositae (daisy family).

##### 2.1.2. Common names

The plant is called Chrysanthemum in English literature and Ju 菊 in Chinese.

The flower heads used in traditional Chinese medicine are commonly known as Juhua 菊花 or, more specifically in pharmaceutical name, Flos Chrysanthemi (Anonymous, 1995).

Due to the differences in sites of cultivation and processing methods, commodities of this herb are classified into four types (Anonymous, 1977, 1995; Zhang et al., 1990a):

(i) 'Baiju 白菊' – produced by drying the cut stem upside down in shade and then collecting the flower heads when dried; those produced in Anhui Province are known as 'Haoju 毫菊', generally regarded as the best; also produced in Henan Province 'Huaiju 淮菊', Hebei Province 'Qiju 祁菊', and Sichuan Province 'Chuanju 川菊';

(ii) 'Chuju 滁菊' – produced in Anhui Province by drying under the sun after fumigation with sulfur;

(iii) 'Gongju 貢菊' – produced in Henan Province by drying over fire;

(iv) 'Hangju 杭菊' – produced in Zhejiang Province by drying under the sun after steaming with boiling water.

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### 2.1.3. Botanical description of the plant

The plant is a perennial herb, 50-140 cm high, densely covered with white villous hairs. Leaves alternate, ovate or ovate-lanceolate, 3.5-5 cm long, 3-4 cm wide, obtuse at apex, subcordate at base, deeply lobed and serrate along margins. Flower heads terminal or axillary, 2.5-5 cm across; flowers associated with bracts, dimorphic, the outer flowers ligulate, female, the corolla white, yellow, pink or lilac, the central flowers tubular, bisexual, the corolla yellow; ovaries inferior. Flowering mainly from September to November and setting fruits in October and November.

### 2.1.4. Description of the herb

Heads dried, bearing several layers of ligulate flowers toward the outer circumference and many tubular flowers in the center; the receptacle protected by an involucre composed of 3-4 layers of phyllaries; fragrant, with a bland of plain to sweet and bitter tastes.

According to the American Herbal Products Association's *Botanical Safety Handbook* (McGuffin et al., 1997), *Chrysanthemum* is classified as Class 1 which is defined as herbs that can be safely consumed when used appropriately.

### C. Condition of Use :

#### Current use of ingredient

Tea brewed with the flower heads of *Dendranthema morifolium* alone or together with tea leaves is a common beverage in the daily life of the Chinese people, particularly those in Hong Kong and Taiwan. Petals of the ligulate flowers are often added to soups and congees, such as the snake soup enjoyed by Chinese communities in the Orient. This herb also is used as medicinal herb with the normal dosage of 5-9 g (Anonymous, 1995).

Soft drinks or herb teas prepared with the flower heads of *Dendranthema morifolium* are popular in the Orient. Instant chrysanthemum teas are also very popular. It is produced by brewing the flower heads with boiling water and then concentrating the extract by heat and finally made into dry granular particles by mixing it with cane sugar (Hu, 1997).

The Vita Herbal Tea Drink is prepared with less than 2 g per litre of this herb as a flavoring agent. The drink is expected to be consumed mainly by Chinese Americans in North America (U.S. and Canada) China Towns.

### D. Basis for the GRAS determination

The GRAS determination is experience based on common use in foods.

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**E. Availability of information**

The search for scientific publications on this safety assessment of this herb and on herbal teas was conducted on the following computer databases:

- (a) Medline of the US National Library of Medicine,
- (b) TCM Database of the Chinese Medicinal Material Research Centre, the Chinese University of Hong Kong,
- (c) CHIMERA, a database on cases of adverse reactions due to Chinese medicines developed by the Chinese Medicinal Material Research Centre, the Chinese University of Hong Kong.

The data and information that are the basis for the determination are available for review and copying by FDA and will be sent to FDA upon request.

**F. Sign and Date**

Based on the review of generally available data and the expert consultation provided by Prof. Paul But from the Chinese Medicinal Material Research Centre, the Chinese University of Hong Kong, I believe the use of Chrysanthemum in the Vita Herbal Tea Drink is safe for human consumption; and therefore is exempted from pre-market approval.

Notifier : \_\_\_\_\_

(Mr. Joe Ho, Technical Director of Vitasoy International Holdings Ltd.)

Date : 4 November, 1998.

**II. SUMMARY OF IDENTIFICATION AND SPECIFICATION**

**1. Phytochemistry**

Flower heads of two cultivars of *Dendranthema morifolium*, namely 'Peacock' and 'Regal Anne', showed the presence of four flavonoids: cosmosiin, diosmetin-7-O- $\beta$ -D-glucoside, luteolin-7-O- $\beta$ -D-glucoside, and tilianin (Asen et al., 1975).

Petals (of the ligulate flowers) of *Dendranthema morifolium* var. *sinense* f. *esculentum* contain 12 normal saturated hydrocarbons (n-nonadecane, n-eicosane, n-heneicosane, n-docosane, n-pentacosane, n-hexacosane, n-heptacosane, n-octacosane, n-nonacosane, n-triacontane, n-hentriacontane and n-tritriacontane), five fatty acids (behenic acid, lignoceric acid, linoleic acid, palmitic acid and stearic acid), 11 free amino acids (alanine, arginine, aspartic acid, glucine, glycine, isoleucine, leucine, proline, serine, threonine and valine), and campesterol, stigmasterol,  $\beta$ -sitosterol,  $\alpha$ -amyrin,  $\beta$ -amyrin and apigenin (Takahashi et al., 1975; Takahashi & Sato, 1979 a,b).

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The petals also contain  $\beta$ -elemene, glucose, luteolin, thymol, n-tricosane and F2a-prostaglandin (Takahashi & Sato, 1978; Tamai et al., 1982).

Luteolin with antibacterial, anti-inflammatory, antitussive and antineoplastic actions was found in the flower heads, ranging from 0.031-0.048% in the white flower cultivars to 0.051-0.066% in the yellow cultivars (Shen & Xing, 1990).

Volatile oil of the flower head contains borneol, bornyl acetate and chrysanthemon (Kotake & Nonaka, 1957). However, contents of the volatile oil in the flower heads were found affected by methods of processing. Flower heads dried by placing the cut stem upside down in shade contain the highest amount of volatile oil (0.68-0.85%), whereas those dried by steaming or pretreated with sulfur fumigation contain only 0.115-0.328% of volatile oil (Zhang et al., 1990a). Similar results were also reported by Zhang et al. (1990b) who showed that flower heads processed by steaming have the lowest percentage of volatile oil and also the lowest percentage of camphor and borneol in the volatile oil.

Analysis of the nutritive components of the flower heads of *Dendranthema morifolium* showed the presence, in both the herb and its water extract, of potassium, calcium, magnesium, iron, nickel, copper, zinc and 18 amino acids. Vitamin E (122 mg/kg in the herb and 11.25 mg/kg in the water extract) was also isolated (Xing and Shen, 1989).

Carbohydrate content in the ray florets of *Dendranthema morifolium* varies with different stages of development in the florets. Total and reducing sugars increase until the ray florets attain their maximal expansion and peak fresh and dry weights. Senescing stages of ray florets are characterized by decreases in fresh and dry weights and loss of metabolites (Saradhi & Ram, 1987). Hence quality and nutritive and medicinal values of the flower heads are affected by both the stage of collection and drying processes.

The major anthocyanin pigment in three red cultivars of *Dendranthema morifolium* was identified as cyanidin 3-O-(6-O-malonyl- $\beta$ -D-glucopyranoside) (Saito et al. 1988).

## **2. Method of Manufacture**

In Asian countries, Chrysanthemum is processed by drying.

## **3. Pharmacology**

Scientific studies have shown antibacterial, antifungal, hypotensive, gonadotropin-like, and Anti-HIV effects (Hsu et al., 1986; Hu et al., 1994; Sung, 1996). The triterpene alcohols of the flower heads showed strong anti-inflammatory activity (Akihisa et al., 1996).

#### **4. Specification for food-grade material**

The herb remains clean and not contaminated.

### **III. SUMMARY OF SELF LIMITING LEVELS OF USE**

If Chrysanthemum is added to food above its self-limiting level, the food becomes unappealing and has medicinal purpose for general consumption.

### **IV. COMMON USE GRAS DETERMINATION**

#### **1. Technical evidence of safety**

##### **1.1. History of use (Folk medicinal uses)**

Flower heads of *Dendranthema morifolium* have been used for thousands of years by the Chinese as both food supplement and medicine. In the Divine Plowman's Herbal, which was compiled between 200 B.C. and 200 A.D., the herb was already registered in the superior category. It is used as a single item or in combination with other herbs in polyprescriptions. It has a slightly 'cold' property, and is reputedly good for dispersing 'wind', clearing 'heat', calming the liver and brightening the eyes. It is most commonly prescribed in common cold due to 'pathogenic wind-heat', headache with vertigo, acute conjunctivitis, blurry eye-sight, and hypertension.

##### **1.2. Toxicity assessment**

###### **1.2.1. Acute toxicity**

Flower heads of *Dendranthema morifolium* show very low toxicity. Hot water extracts of the flower heads given to mice at 100 g equivalent of starting material/kg body weight via intragastric administration showed a low mortality rate; eight of the ten mice survived. Similar administration of the aqueous extract of the flower heads at the same dosage led to no death in mice.

LD<sub>50</sub> of the volatile oil of the aerial parts (leaf and stem) of the plant in mice was 1.35±0.13 g/kg i.p. (Chang & But, 1987); but this piece of information bears little relevance to the flower heads.

###### **1.2.2. Subacute toxicity**

Intragastric administration of the aqueous extracts to rabbits at doses equivalent to 20 g of crude drug/kg for 14 days did not cause significant changes in the ECG, BSP and phenol red excretion on the seventh day of treatment. Then death was seen on the 10th day (Chang & But, 1987). Injection of the volatile oil in mice at 0.4 mg/day i.p. for 10 days did not alter the blood picture or liver function (Chang & But, 1987).

## 2. Safety assessment

According to the American Herbal Products Association's *Botanical Safety Handbook* (McGuffin et al., 1997), chrysanthemum is classified as Class 1 which is defined as herbs that can be safely consumed when used appropriately.

Toxicity tests in animals showed that chrysanthemum is very safe. Contact dermatitis is known only from the adverse reactions to direct contacts with the leaves of fresh plants. Reports have shown, however, upper abdominal pain or diarrhea in individual patients receiving *concentrated* decoction or fluid extract tablets of this herb (Chang & But, 1987).

Chrysanthemum is a very common dietary supplement and is commonly used in preparing herbal teas in Hong Kong and southern China (Hu, 1997). Its safety is well-accepted and the herb is on the GRAS list and regarded as safe in many Oriental and Western countries (De Smet, 1993). The herb used by Vitasoy is the 'Hangju 杭菊' cultivar. The low concentration of this herb extract in the Herb Tea to be manufactured by Vitasoy is not expected to cause any adverse reaction upon normal consumption.

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**I. GRAS EXEMPTION CLAIM**

2

**A. Name and Address of Notifier :**

Mr. Joe Ho (Technical Director)  
Vitasoy International Holdings Ltd., 1, Kin Wong Street, Tuen Mun, New Territories, Hong Kong.

**B. Name of Substance :**

1. **Licorice** is commonly known as Ganciao 甘草 in Chinese.

2. **Description**

This herb refers to the root and rhizome of *Glycyrrhiza uralensis* Fisher and related species.

**2.1. Botanical**

**2.1.1. Botanical name**

*Glycyrrhiza uralensis* Fisher, *G. glabra* L., and *G. inflata* Batalin of the Leguminosae (pea family).

**2.1.2. Common names**

The plant is called Licorice in English and Ganciao in Chinese. The root and rhizome used in Chinese medicine are commonly known as Ganciao 甘草 or more specifically in pharmaceutical name as Radix Glycyrrhizae (Hsu et al., 1986; Anonymous, 1995).

**2.1.3. Botanical description of the plant**

Perennial herb, 30–70 (–100) cm tall. Rhizome cylindrical, the main root very long, thick, the outer skin reddish brown or dark brown. Erect stem, woody, covered with short white hair or glandular hair. Leaves alternate, even-pinnate; the leaflets 4–8 pairs, oval, 2–5 .5 cm long, 1.5–3 cm wide, with pointed apex and round base. Flowering in June to July (Hsu et al., 1986).

**2.1.4. Description of the herb**

The root collected are processed by sun-dried method or stir-fried with honey method. They are long cylindrical, 30–120 cm long and 0.6–3.3 cm in diameter, reddish brown, brown or grayish brown on the outer skin, yellow inside (Hsu et al., 1986).

**C. Condition of Use :**

**Current use of ingredient**

The herb is widely used in both the Orient and Western countries as a dietary supplement and a medicinal herb with a normal dosage of 1.5 - 9 g (Anonymous 1995). It is found in many food items, including candies, cough drops and syrups, and herb teas. The Vita Herbal Tea Drink in a 250 mL tetrapack is prepared with less than 2 g per litre of this herb as a flavoring agent. The drink is expected to be consumed mainly by Chinese Americans in North America (U.S. and Canada) China Towns.

**D. Basis for the GRAS determination**

The GRAS determination is experience based on common use in foods.

**E. Availability of information**

The search for scientific publications on this safety assessment of this herb and on herbal teas was conducted on the following computer databases:

- (a) Medline of the US National Library of Medicine,
- (b) TCM Database of the Chinese Medicinal Material Research Centre, the Chinese University of Hong Kong,
- (c) CHIMERA, a database on cases of adverse reactions due to Chinese medicines developed by the Chinese Medicinal Material Research Centre, the Chinese University of Hong Kong,

The data and information that are the basis for the determination are available for review and copying by FDA and will be sent to FDA upon request.

**F. Sign and Date**

Based on the review of generally available data and the expert consultation provided by Prof. Paul But from the Chinese Medicinal Material Research Centre, the Chinese University of Hong Kong, I believe the use of Licorice in the Vita Herbal Tea Drink is safe for human consumption; and therefore is exempted from pre-market approval.

Notifier : \_\_\_\_\_

(Mr. Joe Ho, Technical Director of Vitasoy International Holdings Ltd.)

Date : 4 November, 1998.



## **II. SUMMARY OF IDENTIFICATION AND SPECIFICATION**

### **1. Phytochemistry**

Saponins 6-14%: the main constituent is glycyrrhizin ( which is about 50 times sweeter than sugar), which upon hydrolysis yields glycyrrhetic acid and glucuronic acid. Other crude saponins yield glabric acid, gabrolide, and 28-hydroxyglycyrrhetic acid upon hydrolysis. Also licorice-saponins, isoliquiritin apioside, 18 $\alpha$ -glycyrrhizin, apioglycyrrhizin, araboglycyrrhizin.

Flavonoids: liquiritin (its aglycone is liquiritigenin), isoliquiritin (its aglycone is isoliquiritigenin), licoflavone, licoricone, 2-methyl-7-hydroxyisoflavone, licoricidin, licochalcone A, isolicoflavonol, glycyrrhisoflavone.

Coumarin: glycy coumarin, licopyranocoumarin, licocoumarone.

Polysaccharides: glycyrrhizan.

Others: amino acids, glucose, sucrose, mannitol, asparanic acid, glycyrols (Hsu et al., 1986; Kitagawa et al., 1993; Kimura, 1996).

### **2. Method of Manufacture**

In Asian countries, Licorice is processed by drying.

### **3. Pharmacology**

Scientific studies have shown a wide range of bioactivities, including the followings:

- a) Anti-HIV effects (Hatano et al., 1988).
- b) Antioxidant effects (Demizu et al., 1988).
- c) Antimicrobial effects (Demizu et al., 1988).
- d) Antiulcer, antispasmodic, antiinflammatory, antitussive, antiallergic, antidote, adrenocortical, mitogenic and anti-complementary effects (Hsu et al., 1986; Kimura, 1996; Kiyohara et al., 1996).

### **4. Specification for food-grade material**

The herb remains clean and not contaminated.

## **III. SUMMARY OF SELF LIMITING LEVELS OF USE**

If Licorice is added to food above its self-limiting level, the food becomes unappealing and has medicinal purpose for general consumption.

## **IV. COMMON USE GRAS DETERMINATION**

### **1. Technical evidence of safety**

#### **1.1. History of use (Folk medicinal uses)**

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This herb has been used by the Chinese people for over 2,000 years. It was already registered in the 'Divine Plowman's Herbal' compiled between 200 BC and 200 AD. In Chinese medicine, it has a sweet flavor and "neutral" property. It enters the twelve channels. It is reputedly good for supplementing 'spleen', replenishing 'qi', clearing 'heat', removing 'toxin', moistening 'lungs', controlling cough, harmonizing the stomach and spleen, and harmonizing all drugs. It is commonly prescribed in sore throat, carbuncle, toxic swelling, toxicosis in fetuses and children, diarrhea due to spleen-deficiency, thirst due to stomach deficiency, cough due to dry lung palpitations, digestive ulcer, abdominal pain, convulsive diseases, hepatitis, phlegm, common cold, gastrointestinal disorder, palpitation, arrhythmia, epilepsy, and reducing the toxic or drastic actions from other herbs included in multiple-item herbal decoctions.

Contraindications: incompatible with the herbs *Radix Euphorbiae Pekinensis*, *Flos Genkwa* and *Radix Kansui*.

Side effects : Overdose may cause edema, hypertension, hypokalemia.

Normal dosage: 1.5–9 g (Hsu et al., 1986).

## **1.2. Toxicity assessment**

### **1.2.1 Acute toxicity**

No acute toxicity is known.

### **1.2.2 Chronic toxicity**

A single large dose or a subchronic low dose of the herb causes in about 20% of patients edema, dizziness, hypertension, and hypokalemia.

## **2. Safety assessment**

According to the American Herbal Products Association's *Botanical Safety Handbook* (McGuffin et al., 1997), Licorice is classified as Class 1 which is defined as herbs that can be safely consumed when used appropriately.

This herb is widely used in the Orient and the West as both dietary supplement and medicine. It is also commonly used in preparing herbal teas in Hong Kong and southern China (Hu, 1997). Its safety is well-accepted and the herb is on the GRAS list and regarded as safe in many Oriental and Western countries (De Smet, 1993). Excessive use may cause hypokalemia, edema, dizziness, hypertension, mineralcorticoid effects or even, in Japan, hepatitis. However, the diluted concentration of this herb in the Vita Herbal Tea Drink to be manufactured by Vitasoy International Holdings Ltd. is not expected to cause any adverse reaction upon normal consumption. It would be up to the manufacturer to decide if they wish to stress any precaution, although it is generally not necessary for this type of preparation.

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## References:

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- McGuffin M, Hobbs C, Upton R and Goldberg A (eds.) 1997. American Herbal Products Association's *Botanical Safety Handbook*. CRC Press, Boca Raton, pp. 58.

## I. GRAS EXEMPTION CLAIM

3

### A. Name and Address of Notifier :

Mr. Joe Ho (Technical Director)  
Vitasoy International Holdings Ltd., 1, Kin Wong Street, Tuen Mun, New Territories, Hong Kong.

### B. Name of Substance :

1. **Honeysuckle** is commonly known as Jinyinhua 金銀花 in Chinese.

#### 2. Description

The source material of this herb is the flower bud of *Lonicera japonica* Thunberg and related species.

#### 2.1. Botanical

##### 2.1.1. Botanical name

*Lonicera japonica* Thunberg of Caprifoliaceae (honeysuckle family). Flower buds of related species (*L. hypoglauca* Miq. *L. confusa* DC, and *L. dasystyla* Rehd) are also accepted as alternatives (Anonymous, 1995).

##### 2.1.2. Common names

The plant is called Honeysuckle in English literature and Rendong 忍冬 in Chinese. The flower bud used in Chinese medicine is known as Jinyinhua 金銀花 or more specifically in pharmaceutical name as Flos Lonicerae (Hsu et al., 1986; Anonymous, 1995).

##### 2.1.3. Botanical description of the plant

The plant is a vine. Leaves opposite. Flowers arranged in a spike to 15 cm long at the branch tip. Each flower has a short stalk and arises in the axil of a small triangular bract. Flowers bisexual, zygomorphic; calyx hairy, two-lipped, the upper lip longer and three-toothed (the central tooth largest); corolla with a short tube opening by two lips, the upper 3-lobed, the lower 1-lobed, concave and hairy on the outside; stamens four, borne on the corolla tube, yellow; ovary, glabrous, the stigma single (Hong Kong Urban Services Department, 1971).

##### 2.1.4. Description of the herb

The flower buds or newly bloomed flowers are collected and processed by drying method or fuming with sulfur and then drying. The herb (flower bud) is cylindrical, 2-3 cm long, 3 mm across on the upper part and 1.5 mm across on the lower, the outer surface whitish yellow or whitish green, hairy, bearing a calyx greenish in

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color, five-toothed, hairy, 2 mm long, and a corolla tube opening by two lips and enclosing five stamens.

The dried flower buds, cylindrical in shape, curved, 2-3 cm long; upper part thicker, 1.5-3 mm in diameter; yellow or yellowish brown, covered with short and soft hair; fragrant, mildly bitter to taste (Anonymous, 1977).

**C. Condition of Use :**

**Current use of ingredient**

This herb is widely used in herbal medicine (the normal dosage of 6-15 g) (Anonymous 1995) and in making herb teas (Hu, 1997).

The Vita Herbal Tea Drink in a 250 mL tetrapack is prepared with less than 2.5g per litre of this herb as a flavoring agent. The drink is expected to be consumed mainly by Chinese Americans in North America (U.S. and Canada) China Towns.

**D. Basis for the GRAS determination**

The GRAS determination is experience based on common use in foods.

**E. Availability of information**

The search for scientific publications on this safety assessment of this herb and on herbal teas was conducted on the following computer databases:

- (a) Medline of the US National Library of Medicine,
- (b) TCM Database of the Chinese Medicinal Material Research Centre, the Chinese University of Hong Kong,
- (c) CHIMERA, a database on cases of adverse reactions due to Chinese medicines developed by the Chinese Medicinal Material Research Centre, the Chinese University of Hong Kong,

The data and information that are the basis for the determination are available for review and copying by FDA and will be sent to FDA upon request.

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## F. Sign and Date

Based on the review of generally available data and the expert consultation provided by Prof. Paul But from the Chinese Medicinal Material Research Centre, the Chinese University of Hong Kong, I believe the use of Honeysuckle in the Vita Herbal Tea Drink is safe for human consumption; and therefore is exempted from pre-market approval.

Notifier : \_\_\_\_\_

(Mr. Joe Ho, Technical Director of Vitasoy International Holdings Ltd.)

Date : 4 November, 1998.

## II. SUMMARY OF IDENTIFICATION AND SPECIFICATION

### 1. Phytochemistry

This herb mainly composes of chlorogenic acid, isochlorogenic acid, neochlorogenic acid, 4-O-caffeoylquinic acid, luteolin, lonicerin, inositol (sweet component) and loniceroside A (Budavari 1989; Chang and But, 1987; Kimura, 1997). The major constituents in the essential oil are linalool, geraniol, aromadendrene and eugenol (Budavari, 1989; Wang et al., 1992).

For the details :

#### *Chlorogenic acid*

*Chemical name :* 3-[[3-(3,4-Dihydroxyphenyl)-1-oxo-2-propenyl]oxy]-1,4,5-trihydroxycyclohexane-carboxylic acid

*CAS :* [ 327-97-9]

*Molecular formula :* C<sub>16</sub>H<sub>18</sub>O<sub>9</sub>

*Others :* (i) it forms caffeic acid on hydrolysis.  
(ii) it is an important factor in plant metabolism.

*Isochlorogenic acid* is one of the isomers of chlorogenic acid.

*Neochlorogenic acid* is one of the isomers of chlorogenic acid.

*4-O-caffeoylquinic acid* is isomeric with chlorogenic acid.

#### *Luteolin*

*Chemical name :* 2-(3,4-Dihydroxyphenyl)-5,7-dihydroxy-4H-1-benzopyran-4-one

*CAS :* [491-70-3]

*Molecular formula :* C<sub>15</sub>H<sub>10</sub>O<sub>6</sub>

*Others :* it is found in many plants in glycosidic combination.

#### *Inositol*

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*Chemical name* : hexahydroxycyclohexane  
*CAS* : [87-89-8]  
*Molecular formula* :  $C_6H_{12}O_6$   
*Others* : (i) it is a sugar;  
(ii) therapeutic category : Vitamin B complex; lipotropic.

#### **Linalool**

*Chemical name* : 3,7-Dimethyl-1,6-octadien-3-ol  
*CAS* : [78-70-6]  
*Molecular formula* :  $C_{10}H_{18}O$   
*Others* : (i) it is the chief constituent of linaloe oil.  
(ii) use : in perfumery instead of bergamot or French lavender oil.

#### **Geraniol**

*Chemical name* : 3,7-Dimethyl-2,6-octadien-1-ol  
*CAS* : [106-24-1]  
*Molecular formula* :  $C_{10}H_{18}O$   
*Others* : (i) isomeric with linalool  
(ii) use : in perfumery; as insect attractant.

#### **Eugenol**

*Chemical name* : 2-Methoxy-4-(2-propenyl)phenol  
*CAS* : [97-53-0]  
*Molecular formula* :  $C_{10}H_{12}O_2$   
*Others* : (i)  $LD_{50}$  orally in rats, mice: 2680, 3000 mg/kg (Hagan et al., 1965)  
(ii) use : in perfumery instead of oil of cloves; manufacture vanillin; as insect attractant.  
(iii) therap : Analgesic (dental).

### **2. Method of Manufacture**

In Asian countries, Honeysuckle is prepared by drying in shade.

### **3. Pharmacology**

Scientific studies have shown antibacterial, antiviral, antispasmodic, hepatoprotective, stomachic and diuretic effects (Hsu et al., 1986; Kimura, 1997). Polyphenolic compounds in the herb have inhibitory effect on platelet activation and cytoprotective effect on hydrogen peroxide-induced cell injury (Chang & Hsu, 1992).

### **4. Specification for food-grade material**

Flowe bud remains unopen, clean and not contaminated.

## **III. SUMMARY OF SELF LIMITING LEVELS OF USE**

If Honeysuckle is added to food above its self-limiting level, the food becomes unappealing and has medicinal purpose for general consumption.

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#### **IV. COMMON USE GRAS DETERMINATION**

##### **1. Technical evidence of safety**

###### **1.1. History of use (Folk medicinal uses)**

Honeysuckle has been using in Chinese medicine since the 6<sup>th</sup> Century. It has sweet flavor and a 'cold' property. It enters the channels of lung, stomach, heart, and spleen meridians. It is reputedly good for removing toxic heat, being antipyretic, detoxicant and having anti-inflammatory actions. It is most commonly prescribed in fever due to common cold, dermal eruption, carbuncle, malignant ulcer, dysentery, toxic (virulent) swelling and toxic heat (Anonymous, 1977; Chang and But, 1987).

Dosage: commonly use 6-15 g per dose (Anonymous, 1995); for pyrogenic diseases 30 g per dose; for serious cases 60-90 g per dose and may be increased to 120 g.

###### **1.2 Toxicity assessment**

###### **1.2.1. Acute toxicity**

Intragastric administration of the aqueous extract of the herb to rabbits and dogs produced no significant toxic effects, nor any alterations in the respiration, blood picture, and urine output. The LD<sub>50</sub> of this extract was determined to be 53 g/kg s.c. in mice (Chang & But, 1987).

Allergic reactions were associated with chlorogenic acid, but these reactions were absent with oral administration, since intestinal secretion would transform it into a non-allergenic substance (Freedman et al., 1964). Contact dermatitis has also been reported from direct contact with the plant (Webster, 1993); but this problem has no relevance to the use of the flower buds in herbal teas.

###### **1.2.2 Chronic toxicity**

No data on chronic toxicity is available.

##### **2. Safety assessment**

According to the American Herbal Products Association's *Botanical Safety Handbook* (McGuffin et al., 1997), honeysuckle is classified as Class 1 which is defined as herbs that can be safely consumed when used appropriately.

The herb is indeed very commonly used in the preparation of herbal drinks. No serious side effect is known. In addition, Honeysuckle has a substantial history of consumption for food use since the 6<sup>th</sup> Century by a significant number of Chinese consumers. Normal uses of this herb in Chinese medicine has not shown any adverse effects.

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The diluted concentration of this herb in the Vita Herbal Tea Drink to be manufactured by Vitasoy International Holdings Ltd. is expected to be safe upon normal consumption.

## References:

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- Anonymous. 1995. *Pharmacopoeia of the People's Republic of China (1995 edition)*. Guangdong Technology Press & Chemical Industry Press, Guangzhou, Vol. 1, pp. 189-190.
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- Kimura T. 1997. *Lonicera japonica* Thunb. (Caprifoliaceae). In: But PPH, Kimura T, Guo JX and Sung CK (eds.) *International Collation of Traditional and Folk Medicine*. Vol. 2. World Scientific, Singapore, pp. 147-148.
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- Webster RM. 1993. Honeysuckle contact dermatitis. *Cutis* 51: 424.

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# I. GRAS EXEMPTION CLAIM

## A. Name and Address of Notifier :

Mr. Joe Ho (Technical Director)  
Vitasoy International Holdings Ltd., 1, Kin Wong Street, Tuen Mun, New Territories, Hong Kong.

## B. Name of Substance :

1. **Lophatherum** is commonly known as Danzhuye 淡竹葉 in Chinese.

### 2. **Description**

This herb refers to the whole plant or just the leaf of *Lophatherum gracile* Brongn.

#### 2.1. **Botanical**

##### 2.1.1. **Botanical name**

*Lophatherum gracile* Brongn. of Poaceae (grass family).

##### 2.1.2. **Common names**

The plant is called Lophatherum in English and Danzhuye in Chinese.

The whole plant used in Chinese medicine is commonly known as Danzhuye 淡竹葉 or more specifically in pharmaceutical name as Herba Lophartheri (Namba et al., 1980; Hsu et al., 1986; Anonymous, 1995).

##### 2.1.3. **Botanical description of the plant**

The culms are tufted, erect and 40–100 cm tall. Leaf-blade is lanceolate, 20 cm long and 5 cm wide, with prominent longitudinal and lateral veins forming rectangular patterns, the base narrowing to a stalk; the ligule is minute and 0.5 mm wide. The inflorescence is a spike-like panicle, 20 cm long with branches 5–10 cm long. Each spikelet is 7–10 mm long and borne on a short stalk; the glumes are boat-shaped; the lemma is 6–7 mm long, with a short terminal awn; the palea is narrow, with a tuft of awns at the apex (Griffiths, 1983).

##### 2.1.4. **Description of the herb**

The leaf collected are processed by drying. The herb 25–75 cm. Stem, cylindrical in shape, with node, yellowish green in color. The leaves have rectangular venation patterns. Fragrant, mild flavor. Herb samples in Hong Kong herbshops consist mainly of the leaves and are sold in either small bundles or as loose leaf fragments (Namba et al., 1980).

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**C. Condition of Use :**

**Current use of ingredient**

The herb is very commonly used in making herb teas (Hu, 1997) and also is commonly used as a medicinal herb (normal dosage: 6-9 g) (Anonymous 1995). The Vita Herbal Tea Drink in a 250 mL tetrapack is prepared with less than 2 g per litre of this herb as a flavoring agent. The drink is expected to be consumed mainly by Chinese Americans in North America (U.S. and Canada) China Towns.

**D. Basis for the GRAS determination**

The GRAS determination is experience based on common use in foods.

**E. Availability of information**

The search for scientific publications on this safety assessment of this herb and on herbal teas was conducted on the following computer databases:

- (a) Medline of the US National Library of Medicine,
- (b) TCM Database of the Chinese Medicinal Material Research Centre, the Chinese University of Hong Kong,
- (c) CHIMERA, a database on cases of adverse reactions due to Chinese medicines developed by the Chinese Medicinal Material Research Centre, the Chinese University of Hong Kong,

The data and information that are the basis for the determination are available for review and copying by FDA and will be sent to FDA upon request.

**F. Sign and Date**

Based on the review of generally available data and the expert consultation provided by Prof. Paul But from the Chinese Medicinal Material Research Centre, the Chinese University of Hong Kong, I believe the use of Lophatherum in the Vita Herbal Tea Drink is safe for human consumption; and therefore is exempted from pre-market approval.

Notifier : \_\_\_\_\_

(Mr. Joe Ho, Technical Director of Vitasoy International Holdings Ltd.)

Date : 4 November, 1998

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## II. SUMMARY OF IDENTIFICATION AND SPECIFICATION

### 1. **Phytochemistry**

Arundoin, cylindrin, taraxerol, friedelin (Hsu et al., 1986; But, 1996).

For the details:

#### ***Arundoin***

*Chemical name:* D:C-Friedo-B':A'-neogammacer-9(11)-ene,3-methoxy-(3, $\beta$ )  
*CAS:* [4555-56-0]

#### ***Cylindrin***

*Chemical name:* D:C-Friedo-B':A'-neogammacer-9(11)-ene,3-methoxy-(3.  
 $\beta$ .,8. $\beta$ .,13. $\beta$ .,14. $\alpha$ .,17. $\beta$ .,18. $\alpha$ .,21.  $\beta$ .)  
*CAS:* [17904-55-1]

#### ***Taraxerol***

*Chemical name:* (3 $\beta$ )-D-Friedoolean-14-en-3-ol; iso-olean-14-en-3 $\beta$ -ol  
*CAS:* [127-22-0]  
*Molecular formula:* C<sub>30</sub>H<sub>50</sub>O

#### ***Friedelin***

*Chemical name:* D: A-Friedooleanan-3-one  
*CAS:* [559-74-0]  
*Molecular formula:* C<sub>30</sub>H<sub>50</sub>O  
*Others:* it is major triterpene constituent of cork.

### 2. **Method of Manufacture**

In Asian countries, Lophatherum is processed by drying.

### 3. **Pharmacology**

Scientific studies have shown antipyretic and diuretic effects (But, 1996).

### 4. **Specification for food-grade material**

The herb remains clean and not contaminated.

## III. **SUMMARY OF SELF LIMITING LEVELS OF USE**

If Lophatherum is added to food above its self-limiting level, the food becomes unappealing and has medicinal purpose for general consumption.

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#### IV. COMMON USE GRAS DETERMINATION

##### 1. Technical evidence of safety

###### 1.1. History of use (Folk medicinal uses)

The herb has been used for over 500 years in Chinese medicine (Namba et al., 1980), and is commonly prescribed in treating 'hot' syndromes in Chinese medicine. It is bitter and has a 'cold' property. It enters the channels of heart, stomach and small intestine. It is reputedly good for clearing heat and promoting urination. It is commonly prescribed in febrile disease, pharyngitis, stomatitis, buccal sore, swollen gums, hematuria, oliguria, and urinary tract infection.

Contraindications: Use with care during pregnancy.

Normal dosage: 6-9 g (Hsu et al., 1986).

###### 1.2. Toxicity assessment

###### 1.2.1. Acute toxicity

LD<sub>50</sub> of the water extract in mice is 64.5 g/kg p.o. (Hsu et al., 1986) and of the methanol-water extract in mice is estimated to be higher than 1g/kg i.p. (Nakanishi et al., 1965).

###### 1.2.2. Chronic toxicity

No data on chronic toxicity is available.

##### 2. Safety assessment

The herb has been used for over 500 years in Chinese medicine (Namba et al., 1980), and is commonly prescribed in treating 'hot' syndromes in Chinese medicine and used in making herbal teas (Hu, 1997). No adverse reactions to this herb is expected, unless consumed in large quantities during pregnancy. The diluted concentrations in the proposed Vita Herbal Tea Drink to be manufactured by Vitasoy International Holdings Ltd. would be unlikely to cause any side effects.

#### References:

- Anonymous. 1995. *Pharmacopoeia of the People's Republic of China (1995 edition)*, Guangdong Technology Press & Chemical Industry Press, Guangzhou, Vol. 1, p. 288-289.
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**I. GRAS EXEMPTION CLAIM**

**A. Name and Address of Notifier :**

Mr. Joe Ho (Technical Director)  
Vitasoy International Holdings Ltd., 1, Kin Wong Street, Tuen Mun, New Territories, Hong Kong.

**B. Name of Substance :**

1. **Jellywort** is commonly known as Liangfencao 涼粉草.

2. **Description**

The herb refers to the whole plant of *Mesona chinensis* Benth. It is known as Liangfencao 涼粉草 or Xiancao 仙草 in Chinese.

**2.1. Botanical**

**2.1.1. Botanical name**

*Mesona chinensis* Benth., a member of the Lamiaceae (mint family). It is also identified by some authors as *M. procumbens* Hemsley (Chiu, 1991). However, the Flora of China (Li & Hedge, 1994) concluded that the two names actually refer to the same species.

**2.1.2. Common names**

The plant is called Jellywort or Chinese Mesona in English literature, and Liangfencao 涼粉草 in Chinese. The dried herb Liangfencao in Chinese medicine is also more specifically called by the pharmaceutical name Herba Mesonae Chinensis.

**2.1.3. Botanical description of the plant**

The plant is herbaceous, erect or straggling with erect branches, to 50 cm high, the stem tetragonal, hairy. Leaves opposite, simple, oval, 3-7 x 1-3 cm, the apex acute, the base acute-tapering to the leaf stalk, the margins toothed, the leaf stalks to 1 cm long. Flowers arranged in form of a spike of up to 15 cm long. Each flower has a short stalk and arises in the axil of a small triangular bract, bisexual, zygomorphic; calyx hairy, two-lipped, the upper lip longer and three-toothed (the central tooth largest); corolla with a short tube opening by two lips, the upper 3-lobed, the lower 1-lobed, concave and hairy on the outside; stamens four, protruding from the corolla; ovary superior, four-lobed and four-celled, the style single, flattened, topped by a two-lobed stigma. Fruit of four nutlets 0.7 - 0.8 cm long, enclosed in the enlarged and wrinkled calyx. Flowering in autumn and early winter (Thrower, 1984).

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#### **2.1.4. Description of the herb**

The whole plants collected are processed by sun-dried method. The herb is partially dried and then allowed to ferment briefly, followed by drying completely. In the dried herb, the stem is square in cross-section, covered with grayish brown long hair, dark brown or black in color; the leaves are oval-shaped, covered with long hair on both surfaces, also dark brown or black in color. Flowers are usually absent and slightly fragrant, with mild sweet and bitter tastes (Jiangsu New Medical College, 1977).

#### **C. Condition of Use :**

##### **Current use of ingredient**

This herb is mostly used to make herb teas, jelly and medicinal herb (with the dosage of 12-30 g), and such products are very common in China, Hong Kong and Taiwan (Chiu, 1991). The Vita Herbal Tea Drink in a 250 mL tetrapack is prepared with less than 2 g per litre of this herb as a flavoring agent. The drink is expected to be consumed mainly by Chinese Americans in North America (U.S. and Canada) China Towns.

#### **D. Basis for the GRAS determination**

The GRAS determination is experience based on common use in foods.

#### **E. Availability of information**

The search for scientific publications on this safety assessment of this herb and on herbal teas was conducted on the following computer databases:

- (a) Medline of the US National Library of Medicine,
- (b) TCM Database of the Chinese Medicinal Material Research Centre, the Chinese University of Hong Kong,
- (c) CHIMERA, a database on cases of adverse reactions due to Chinese medicines developed by the Chinese Medicinal Material Research Centre, the Chinese University of Hong Kong,

The data and information that are the basis for the determination are available for review and copying by FDA and will be sent to FDA upon request.

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## F. Sign and Date

Based on the review of generally available data and the expert consultation provided by Prof. Paul But from the Chinese Medicinal Material Research Centre, the Chinese University of Hong Kong, I believe the use of Jellywort in the Vita Herbal Tea Drink is safe for human consumption; and therefore is exempted from pre-market approval.

Notifier : \_\_\_\_\_

(Mr. Joe Ho, Technical Director of Vitasoy International Holdings Ltd.)

Date : 4 November, 1998.

## II. SUMMARY OF IDENTIFICATION AND SPECIFICATION

### 1. **Phytochemistry**

The herb contains  $\beta$ -sitosterol,  $\beta$ -sitosterolglucoside, and stigmasterol (Li & Chen, 1980).

For the details :

#### ***$\beta$ -Sitosterol***

*Chemical name:* (3 $\beta$ )-Stigmast-5-en-3-ol

*CAS:* [83-46-5]

*Molecular formula:* C<sub>29</sub>H<sub>50</sub>O

*Others:* (i) common sterol in plants.  
(ii) therap.cat: Anticholesteremic, treatment of prostatic adenoma (Budavari 1996).

#### ***Stigmasterol***

*Chemical name:* (3 $\beta$ ,22E)-Stigmasta-5,22-dien-3-ol

*CAS:* [83-48-7]

*Molecular formula:* C<sub>29</sub>H<sub>48</sub>O

*Others:* usually isolated from the phytosterol mixture from soy or calabar beans.

### 2. **Method of Manufacture**

In Asian countries, Jellywort is processed by drying.

### 3. **Pharmacology**

No reference is available.

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#### **4. Specification for food-grade material**

The herb remains clean and not contaminated.

### **III. SUMMARY OF SELF LIMITING LEVELS OF USE**

If Jellywort is added to food above its self-limiting level, the food becomes unappealing and has medicinal purpose for general consumption.

### **IV. COMMON USE GRAS DETERMINATION**

#### **1. Technical evidence of safety**

##### **1.1. History of use (Folk medicinal uses)**

This herb is used in both Chinese food and Chinese medicine.

A decoction of the herb mixed with rice water is used as a cooling drink in Guangdong and Guangxi provinces in China (Chiu, 1991; Li & Hedge, 1994). The water extract will offer a gel which when mixed with starch from rice or sweet potato can be made into a jelly which is black and tastes good if mixed with syrup or ice cream. The optimum condition for extracting the gel is to reflux for four hours with 0.095–0.191 M  $\text{NaHCO}_3$  containing the plant material at 8%. The added starch should be non-waxy without ionic side groups (Li & Chen, 1980). Canned jelly of this herb is available in the name of Grass Jelly in supermarkets in China towns in North America.

In Chinese medicine, it is regarded as astringent and with sweet flavor. It has a “cold property” and is reputedly good for cleansing summer heat, quenching thirst and removing heat toxin. It is commonly prescribed in sunstroke, thirst, hypertension, rheumatism and diabetes. Dosage: 30-60 g (Hsu et al., 1986).

##### **1.2. Toxicity assessment**

###### **1.2.1 Acute toxicity**

No acute toxicity data is available. No adverse reaction is expected for normal doses for normal users. As a herb with ‘cold’ properties, it is generally not used in large quantities by people in debility and during pregnancy.

###### **1.2.2 Chronic toxicity**

No chronic toxicity data is available. No adverse reaction is expected for normal doses for normal users. As a herb with ‘cold’ properties, it is generally not used in large quantities by people in debility and during pregnancy.

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## 2. Safety assessment

The herb is regularly taken by the Chinese people in southern China to prepare teas and jelly. No report of adverse reactions is known. It is very safe. However, the Chinese people normally do not take large amounts of the teas and jelly for prolonged periods of time, especially during pregnancy.

The diluted concentrations in the proposed Vita Herbal Tea Drink to be manufactured by Vitasoy International Holdings Ltd. would be unlikely to cause any side effects.

### References:

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- Li HW and Hedge IC. 1994. Lamiaceae. In: Wu ZY and Raven PH (eds.) *Flora of China*. Science Press & Missouri Botanical Garden, Beijing and St Louis, p. 294.
- Li CY and Chen LH. 1980. The factors in the gel-forming properties of Hsiao-tsao (*Mesona procumbens* Hemsl.). I. Extraction conditions and different starches. *Proceedings of the National Science Council, Republic of China* 4(4): 438-442.
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**I. GRAS EXEMPTION CLAIM**

**A. Name and Address of Notifier :**

Mr. Joe Ho (Technical Director)  
Vitasoy International Holdings Ltd., 1, Kin Wong Street, Tuen Mun, New Territories, Hong Kong.

**B. Name of Substance :**

1. **Mulberry Leaf** is commonly known as Sangye 桑葉 in Chinese.

2. **Description**

The herb is the leaf of *Morus alba* L. (Moraceae).

**2.1. Botanical**

**2.1.1. Botanical name**

The plant is *Morus alba* L. of Moraceae (mulberry family).

**2.1.2. Common names**

The plant is called Mulberry in English literature and Sangshu 桑樹 in Chinese. The leaf used in Chinese medicine is commonly known as Sangye 桑葉 or more specifically in pharmaceutical name as Folium Mori. They are collected in October-November after frost (Hsu et al., 1986; Anonymous, 1995).

**2.1.3. Botanical description of the plant**

A small tree growing to 9.4 m and is a native of Central and Northern China. The bark is a yellowish-brown and very shallowly cracked. The leaves are extremely variable in shape and in size. On a single branch they may be simple, three-lobed or again more compoundly lobed, to 12 cm or more in length and half as wide. The leaf margins are coarsely toothed with irregular teeth. The leaf stalk is hairless and 2-4 cm long. The leaves are alternate, three to five-nerved at the base.

Flowers are unisexual and both sexes are born in stalked spikes in the axils of the leaves. Male spikes are up to 2.5 cm long, the individual flowers are small, numerous, crowded together, the most obvious feature being the numerous stamens on their slender filaments. Female spikes are 1.5 cm-2 cm long, the individual flowers about 0.3 cm long and many densely crowded together in the spike, the calyx is four-part, the sepals inrolled at the tips, the two stigmas are visible protruding from the small green flask-shaped flowers. Flowers appear in February. The fruit is a compound one formed from the fleshy calyces of the whole inflorescence. The mulberries are up to 5 cm long, cylindrical, red or deep purple in color, sweet and succulent (Thrower, 1988).

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#### **2.1.4. Description of the herb**

The leaf collected are processed by sun-drying. Dried leaves usually are curled or crushed, some whole leaves in oval-shaped, 8–13 cm long, 7–11 cm wide, pointed at apex, toothed, yellowish green, shiny at the upper surface, minutely hairy along the veins, lighter color at the lower surface, with dense small hair. Mild fragrant, mildly bitter taste (Hsu et al., 1986).

#### **C. Condition of Use :**

##### **Current use of ingredient**

This herb has been used in Chinese medicine for over two thousand years (dosage of 5-9 g), and is commonly used in making herbal teas in Hong Kong and southern China (Hu, 1997). The Vita Herbal Tea Drink in a 250 mL tetrapack is prepared with less than 1 g per litre of this herb as a flavoring agent. The drink is expected to be consumed mainly by Chinese Americans in North America (U.S. and Canada) China Towns.

#### **D. Basis for the GRAS determination**

The GRAS determination is experience based on common use in foods.

#### **E. Availability of information**

The search for scientific publications on this safety assessment of this herb and on herbal teas was conducted on the following computer databases:

- (a) Medline of the US National Library of Medicine,
- (b) TCM Database of the Chinese Medicinal Material Research Centre, the Chinese University of Hong Kong,
- (c) CHIMERA, a database on cases of adverse reactions due to Chinese medicines developed by the Chinese Medicinal Material Research Centre, the Chinese University of Hong Kong,

The data and information that are the basis for the determination are available for review and copying by FDA and will be sent to FDA upon request.

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**F. Sign and Date**

Based on the review of generally available data and the expert consultation provided by Prof. Paul But from the Chinese Medicinal Material Research Centre, the Chinese University of Hong Kong, I believe the use of Mulberry leaf in the Vita Herbal Tea Drink is safe for human consumption; and therefore is exempted from pre-market approval.

Notifier : \_\_\_\_\_

(Mr. Joe Ho, Technical Director of Vitasoy International Holdings Ltd.)

Date : 4 November, 1998.

**II. SUMMARY OF IDENTIFICATION AND SPECIFICATION**

**1. Phytochemistry**

Triterpinoids: amyrin, betulinic acid.

Prenylfavones: morusin, cyclomorusin, kuwanons (moracenins and albanins).

Coumarins: umbelliferone.

Others: rutin, quercetin, isoquercitrin, moracetin, astragalin,  $\beta$ -sitosterol,  $\beta$ -sitosterol  $\beta$ -D-glucoside, campesterol, quercetin 3-*O*-(6''-*O*-acetyl)- $\beta$ -D-glucoside, astragalin, kaempferol 3-*O*-(6''-*O*-acetyl)- $\beta$ -D-glucoside, and fagomine (Onogi et al., 1993; Chen et al., 1995b; Kimura, 1996).

For the details:

***Amyrin***

***$\alpha$ -Amyrin***

Chemical name: Urs-12-en-3 $\beta$ -ol

CAS: [638-95-9]

Molecular formula: C<sub>30</sub>H<sub>50</sub>O

Others: (i) it occurs mostly as acetate in latex of rubber trees.

***$\beta$ -Amyrin***

Chemical name: Olean-12-en-3 $\beta$ -ol

CAS: [559-70-6]

Molecular formula: C<sub>30</sub>H<sub>50</sub>O

Others: (i)  $\beta$ -Amyrin occurs together with  $\alpha$ -amyrin.

***Betulinic acid***

Chemical name: Lup-20(29)-en-28-oic acid, 3-hydroxy-, (3. $\beta$ .)-

CAS: [472-15-1]

***Morusin***

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*Chemical name:* 4H,8H-Benzo[1,2-b:3,4-b']dipyrano-4-one,2-(2,4-dihydroxy-phenyl)-5-hydroxy-8,8-dimethyl-3-(3-methyl-2-butenyl)  
*CAS:* [62596-29-6]

***Cyclomorusin***

*Chemical name:* 3H,7H,8H-Bis[1]benzopyrano[4,3-b:6',5'-e]pyran-7-one,6,11-dihydroxy-3,3-dimethyl-8-(2-methyl-1-propenyl)  
*CAS:* [62596-34-3]

***Umbelliferone***

*Chemical name:* 7-Hydroxy-2H-1-benzopyran-2-one  
*CAS:* [93-35-6]

*Molecular formula:* C<sub>9</sub>H<sub>6</sub>O<sub>3</sub>

*Others:* (i) it is the aglucon of skimmin which is present in many plants.  
(ii) used in sunscreen lotions and creams; and as blood-brain barrier probe.

***Rutin***

*Chemical name:* 3-[[6-O-(6-Deoxy- $\alpha$ -L-mannopyranosyl)- $\beta$ -D-glucopyranosyl]oxy]-2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4H-1-benzopyran-4-one

*CAS:* [153-18-4]

*Molecular formula:* C<sub>27</sub>H<sub>30</sub>O<sub>16</sub>

*Others:* (i) found in many plants, especially the buckwheat plant.  
(ii) LD<sub>50</sub> i.v. in mice: 950 mg/kg (propylene glycol soln).  
(Budavari et al., 1996)  
(iii) therap cat. : capillary protectant.

***Quercetin***

*Chemical name:* 2-(3,4-Dihydroxyphenyl)-3,5,7-trihydroxy-4H-1-benzopyran-4-one

*CAS:* [117-39-5]

*Molecular formula:* C<sub>15</sub>H<sub>10</sub>O<sub>7</sub>

*Others:* (i) it is widely distributed in the plant kingdom, especially in rinds and barks, in clover blossoms and in ragweed pollen.  
(ii) toxicity data: (Sullivan, 1951)

***Isoquercitrin***

*Chemical name:* 2-(3,4-Dihydroxyphenyl)-3-( $\beta$ -D-glucofuranosyloxy)-5,7-dihydroxy-4H-1-benzopyran-4-one

*CAS:* [21637-25-2]

*Molecular formula:* C<sub>21</sub>H<sub>20</sub>O<sub>12</sub>

***Astragalin***

*Chemical name:* 4H-1-Benzopyran-4-one,3-( $\beta$ -D-glucopyranosyloxy)-5,7-dihydroxy-2-(4-hydroxyphenyl)-

*CAS:* [480-10-4]

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### ***β-Sitosterol***

*Chemical name:* (3β)-Stigmast-5-en-3-ol

*CAS:* [83-46-5]

*Molecular formula:* C<sub>29</sub>H<sub>50</sub>O

*Others:* (i) common sterol in plants.  
(ii) therap cat: anticholesteremic, treatment of prostatic adenoma.  
(Budavari et al., 1996)

### ***Campesterol***

*Chemical name:* (24R)-Ergost-5-en-3β-ol

*CAS:* [474-62-4]

*Molecular formula:* C<sub>28</sub>H<sub>48</sub>O

### ***Fagomine***

*Chemical name:* 3,4-Piperidinedial, 2-(hydroxymethyl)-, [2R-(2.α., 3.β., 4. α.a.)]

*CAS:* [53185-12-9]

*Molecular formula:* C<sub>27</sub>H<sub>30</sub>O<sub>16</sub>

## **2. Method of Manufacture**

In Asian countries, Mulberry leaf is processed by drying.

## **3. Pharmacology**

Scientific studies have shown the following bioactivities: hypoglycemic, antihypertensive, vasodilator, peripheral parasympathomimetic, analgesic, antitussive, anti-inflammatory and anti-tumor-promoter effects (Chen et al., 1995a,b; Kimura, 1996). Aqueous extracts of the herb showed a weak inhibitory effect on the activities of murine retroviral reverse transcriptase and human DNA polymerases (Ono et al., 1989). The acetylated flavonol glycosides showed moderate inhibitory effects on the water-insoluble glucan synthesis by glucosyltransferase, which may be useful for preventing dental caries (Onogi et al., 1993).

## **4. Specification for food-grade material**

The herb remains clean and not contaminated.

## **III. SUMMARY OF SELF LIMITING LEVELS OF USE**

If Mulberry leaf is added to food above its self-limiting level, the food becomes bitter and has medicinal purpose for general consumption.

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#### IV. COMMON USE GRAS DETERMINATION

##### 1. Technical evidence of safety

##### 1.1. History of use (Folk medicinal uses)

It has a bitter flavor and a "cold" property. It enters the channels of the lung and the liver meridians. It is reputedly good for soothing liver wind and heat, cleansing liver and clearing vision. It is commonly prescribed in headache, hyperemia, thirst, cough, hypertension, arteriosclerosis, influenza, sore eyes, rheumatism and edema.

Normal dosage: 6-12 g

##### 1.2. Toxicity assessment

##### 1.2.1. Acute toxicity

No data on acute toxicity is available.

##### 1.2.2. Chronic toxicity

Administration for 21 days of a 10% extract which is 60 times the human normal usage does not cause any damages to organs, while administration of samples over 250 times causes toxic reaction to the liver, kidney, and lung. Hypersensitivity test using guinea pig showed no effects (Chang & But, 1987).

##### 2. Safety assessment

According to the American Herbal Products Association's *Botanical Safety Handbook* (McGuffin et. al., 1997), Mulberry leaf is classified as Class 1 which is defined as herbs that can be safely consumed when used appropriately.

Oral administration of water extracts of the herb in Chinese medicine has not shown any adverse effects. Muscular injection of a fluidextract of the herb, however, may cause local pain, fever, dizziness, and general malaise (Chang & But, 1987); but this should not be a concern in this review. Contact urticaria with mulberry pollen but not with the leaves was demonstrated in a young boy (Munoz et al., 1995).

The diluted concentration of this herb in the Vita Herbal Tea Drink to be manufactured by Vitasoy International Holdings Ltd. is not expected to cause any adverse reaction upon normal oral consumption.

##### References:

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**I. GRAS EXEMPTION CLAIM**

**A. Name and Address of Notifier :**

Mr. Joe Ho (Technical Director)  
Vitasoy International Holdings Ltd., 1, Kin Wong Street, Tuen Mun, New Territories, Hong Kong.

**B. Name of Substance :**

1. **Frangipani** is commonly known as Jidanhua 雞蛋花 in Chinese.

2. **Description**

The source material of this herb is the flower of *Plumeria rubra* Linnaeus var. *acutifolia* Bailey.

**2.1. Botanical**

**2.1.1. Botanical name**

*Plumeria rubra* L. var. *acutifolia* Bailey is a member of Apocynaceae. Some botanists regards this plant as only a cream-colored cultivar of *Plumeria rubra* L.

**2.1.2. Common names**

The plant is called Frangipani in English literature and Jidanhua in Chinese. The flower used in traditional Chinese medicine are commonly known as Jidanhua 雞蛋花 or more specifically in pharmaceutical name as Flos Plumeriae (Hsu et al., 1986).

**2.1.3. Botanical description of the plant**

A low-branching deciduous tree growing to 5 m in height, with grayish bark and fleshy, cylindrical branches, conspicuously marked with the scars of fallen leaves. All parts exude a white sticky latex when broken. Leaves alternate, crowded at the branch ends, simple, elliptical, leathery, the apex acute, the base also acute, the margins entire, dark green with conspicuous veins. Flowers in clusters at the branch ends, regular and bisexual, fragrant, to about 5 cm across; calyx small, five-parted; corolla of five spreading petals, joined below into a short tube, white with a yellow throat, the petal overlapping regularly right over left; stamens 5, arising near the base of the corolla tube and contained within it; ovary of two partly inferior separate carpels joined by a short style, the stigma two-lobed. Fruit a pair of rather leathery follicles up to 30 x 5 cm, opening to release the winged seeds Flowering in summer (Thrower, 1988).

**2.1.4. Description of the herb**

The flower collected are processed by drying. The dried flowers, yellowish brown in color, slightly fragrant, mildly bitter to taste (Hsu et al., 1986).

**C. Condition of Use :**

**Current use of ingredient**

It is often used as an ingredient in the herb tea called Five Flower Tea, which is the most prevailing home-made herbal tea used in Hong Kong during the hot summer seasons (Hu, 1997). The other four ingredients in this tea are *Bombax ceiba*, *Dendranthema morifolium*, *Lonicera japonica*, and *Sophora japonica* (Hu, 1997).

The Vita Herbal Tea Drink in a 250 mL tetrapack is prepared with less than 2 g per litre of this herb as a flavoring agent. The drink is expected to be consumed mainly by Chinese Americans in North America (U.S. and Canada) China Towns.

**D. Basis for the GRAS determination**

The GRAS determination is experience based on common use in foods.

**E. Availability of information**

The search for scientific publications on this safety assessment of this herb and on herbal teas was conducted on the following computer databases:

- (a) Medline of the US National Library of Medicine,
- (b) TCM Database of the Chinese Medicinal Material Research Centre, the Chinese University of Hong Kong,
- (c) CHIMERA, a database on cases of adverse reactions due to Chinese medicines developed by the Chinese Medicinal Material Research Centre, the Chinese University of Hong Kong,

The data and information that are the basis for the determination are available for review and copying by FDA and will be sent to FDA upon request.

**F. Sign and Date**

Based on the review of generally available data and the expert consultation provided by Prof. Paul But from the Chinese Medicinal Material Research Centre, the Chinese University of Hong Kong, I believe the use of Frangipani in the Vita Herbal Tea Drink is safe for human consumption; and therefore is exempted from pre-market approval.

Notifier: 

(Mr. Joe Ho, Technical Director of Vitasoy  
International Holdings Ltd.)

Date: 4 November, 1998

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## II. SUMMARY OF IDENTIFICATION AND SPECIFICATION

### 1. Phytochemistry

The flowers contain volatile components, including 1,1-diethoxyethane, benzaldehyde, 6-methyl-5-hepten-2-ol, tricyclo[3.2.1.1.0]octane, methyl benzoate, linalool, naphthalene, geraniol, citral, methyl 3-propenylbenzoate, nerolidol, benzyl benzoate, methyl salicylate (Zhu et al., 1993; Pino et al., 1994). Most of these volatile components are expected to be lost during drying of the herb.

Tree bark contains sitosterol, scopoletin, plumieride and fulvoplumierin. The root contains plumericine, isoplumericin,  $\beta$ -dihydropumericin,  $\beta$ -dihydroplumericinic acid, fulvoplumerin and plumeride (Chen & Zhang, 1991). Rubrinol, an antibacterial triterpenoid, together with taraxasteryl acetate, lupeol, stigmasterol, oleanolic acid and cycloart-22-ene-3 $\alpha$ ,25-diol was isolated from the whole plant (Akhtar & Malik, 1994).

For the details:

#### ***Benzaldehyde***

*Chemical name:* Benzoic aldehyde

*CAS:* [100-52-7]

*Molecular formula:* C<sub>7</sub>H<sub>6</sub>O

*Others:*

- (i) artificial essential oil of almond.
- (ii) use : manufacture of dyes, perfumery, cinnamic and mandelic acids, as solvents; in flavors.
- (iii) toxicity data: LD<sub>50</sub> in rats and guinea pigs are 1300 mg/kg and 1000 mg/kg i.g., respectively (Jenner et al., 1964).

#### ***Methyl benzoate***

*Chemical name:* Benzoic acid methyl ester.

*CAS:* [93-58-3]

*Molecular formula:* C<sub>8</sub>H<sub>8</sub>O<sub>2</sub>

*Others:*

- (i) use: in perfumes.
- (ii) toxicity data: LD<sub>50</sub> in rats is 3.43 g/kg i.g. (Smyth et al., 1954).

#### ***Linalool***

*Chemical name:* 3,7-Dimethyl-1,6-octadien-3-ol

*CAS:* [78-70-6]

*Molecular formula:* C<sub>10</sub>H<sub>18</sub>O

*Others:*

- (i) it is the chief constituent of linaloe oil.
- (ii) use : in perfumery instead of bergamot or French lavender oil.

#### ***Naphthalene***

*Chemical name:* Naphthalin

*CAS:* [78-70-6]

*Molecular formula:* C<sub>10</sub>H<sub>8</sub>

*Others:*

- (i) human toxicity : poisoning may occur by ingestion of large doses, inhalation, or skin absorption (Gosselin et al., 1976)

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- (ii) therap. cat. : it has been used as antiseptic (topical & intestinal); anthelmintic (Cestodes).

**Geraniol**

*Chemical name:* 3,7-dimethyl-2,6-octadien-1-ol

*CAS:* [106-24-1]

*Molecular formula:*  $C_{10}H_{18}O$

*Others:* (i) isomeric with linalool  
(ii) use : in perfumery, as insect attractant.

**$\alpha$ -Citral**

*Chemical name:* 3,7-dimethyl-2,6-octadienal

*CAS:* [5392-40-5]

*Molecular formula:*  $C_{10}H_{16}O$

*Others:* (i) citral from natural sources is a mixture of two geometric isomers geranial and neral.  
(ii) use : in synthesis of vitamin A, ionone and methyl-ionone.  
(iii) as a flavor, for fortifying lemon oil, etc.

**Nerolidol**

*Chemical name:* cis-(+)-1,6,10-Dodecatrien-3-ol, 3,7,11-trimethyl, [S-(Z)]-

*CAS:* [142-50-7]

*Molecular formula:*  $C_{15}H_{26}O$

*Others:* (i) found in essential oils from many flowers.

**Benzyl benzoate**

*Chemical name:* Benzoic acid phenylmethyl ester

*CAS:* [120-51-4]

*Molecular formula:*  $C_{14}H_{12}O_2$

*Others:* (i) use: substitute for camphor in celluloid and plastic pyroxylin compounds; in perfume fixative; in confectionery and chewing gum flavors, etc.  
(ii) therap. cat.: scabicide, pediculicide.  
(iii) toxicity data: LD<sub>50</sub> orally in rats, mice, rabbits and guinea pigs are 1.7, 1.4, 1.8 and 1.0 g/kg i.g., respectively (Draize et al., 1948).

**Methyl salicylate**

*Chemical name:* 2-Hydroxybenzoic acid methyl ester

*CAS:* [119-36-8]

*Molecular formula:*  $C_8H_8O_3$

*Others:* (i) use: in perfumery; for flavoring candies, etc.  
(ii) therap. cat.: counterirritant.  
(iii) human toxicity : caution - ingestion of relatively small amounts may cause severe poisoning and death (av. lethal dose: 10 ml in children, 30 ml in adults) (Gosselin et al., 1976).

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**Scopoletin**

*Chemical name:* 7-Hydroxy-6-methoxy-2H-1-benzopyran-2-one

*CAS:* [92-61-5]

*Molecular formula:* C<sub>10</sub>H<sub>8</sub>O<sub>4</sub>

**Plumieride**

*Chemical name:* 1-(β-D-Glucopyranosyloxy)-4α,7α-dihydro-4'-(1-hydroxyethyl)-5'-oxospiro[cyclopenta[c]pyran-7(1H),2'(5'H)-furan]-4-carboxylic acid methyl ester.

*CAS:* [511-89-7]

*Molecular formula:* C<sub>21</sub>H<sub>26</sub>O<sub>12</sub>

**Plumericin**

*Chemical name:* [3aS-(3E,3α,4αβ,7aβ,9aR\*,9bβ)]-3-Ethylidene-3,3a,7a,9b-tetrahydro-2-oxo-2H,4aH-1,4,5-tri-oxadicyclopent[a,hi]indene-7-carboxylic acid methyl ester

*CAS:* [77-16-7]

*Molecular formula:* C<sub>15</sub>H<sub>14</sub>O<sub>6</sub>

**Fulvoplumierin**

*Chemical name:* (E,E)-7-(2-Butenylidene)-1,7-dihydro-1-oxocyclopenta[c]pyran-4-carboxylic acid methyl ester

*CAS:* [20867-01-0]

*Molecular formula:* C<sub>14</sub>H<sub>12</sub>O<sub>4</sub>

*Others:* occurs together with plumieride and plumericin.

**Plumieride**

*Chemical name:* 1-(β-D-Glucopyranosyloxy)-4a,7a-dihydro-4'-(1-hydroxyethyl)-5'-oxospiro[cyclopenta[c]pyran-7(1H),2'(5'H)-furan]-4-carboxylic acid methyl ester

*CAS:* [511-89-7]

*Molecular formula:* C<sub>21</sub>H<sub>26</sub>O<sub>12</sub>

**Lupeol**

*Chemical name:* Lup-20(29)-en-3β-ol

*CAS:* [545-47-1]

*Molecular formula:* C<sub>30</sub>H<sub>50</sub>O

*Others:* it is an abundant plant triterpene.

**Stigmasterol**

*Chemical name:* (3β,22E)-Stigmasta-5,22-dien-3-ol

*CAS:* [83-48-7]

*Molecular formula:* C<sub>29</sub>H<sub>48</sub>O

*Others:* it is isolated from the phytosterol mixture from soy or calabar beans.

**Oleanolic Acid**

*Chemical name:* 3-Hydroxyolean-12-en-28-oic acid

*CAS:* [508-02-1]

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*Molecular formula:* C<sub>30</sub>H<sub>48</sub>O<sub>3</sub>

**2. Method of Manufacture**

In Asian countries, Frangipani is processed by drying.

**3. Specification for food-grade material**

The herb remains clean and not contaminated.

**III. SUMMARY OF SELF LIMITING LEVELS OF USE**

If Frangipani is added to food above its self-limiting level, the food becomes bitter and has medicinal purpose for general consumption.

**IV. COMMON USE GRAS DETERMINATION**

**1. Technical evidence of safety**

**1.1. History of use (Folk medicinal uses)**

In Chinese medicine, it is regarded to have mildly sweet and bitter flavor and considered as non-toxic. It is reputedly good for removing humid heat, moisturizing lung and detoxification. It is commonly prescribed in cough and diarrhea. (Hsu et al., 1986).

**1.2. Toxicity assessment**

**1.2.1. Acute toxicity**

No toxicity data is available for the flowers used as herbs.

**1.2.2. Chronic toxicity**

No toxicity data is available for the flowers used as herbs.

**2. Safety assessment**

No adverse reaction is expected or has been reported for consumption of normal doses of the tea prepared with the herb alone or in combination with other herbs in the Five Flower Tea, which is a common beverage in southern China (Hu, 1997). The diluted concentration of this herb in the Vita Herbal Tea Drink is not expected to cause any adverse reactions upon normal oral consumption.

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## References:

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8

**I. GRAS EXEMPTION CLAIM**

**A. Name and Address of Notifier :**

Mr. Joe Ho (Technical Director)  
Vitasoy International Holdings Ltd., 1, Kin Wong Street, Tuen Mun, New Territories, Hong Kong.

**B. Name of Substance :**

1. Selfheal is commonly known as Xiakucao 夏枯草 in Chinese.

**2. Description**

This herb is the fruitspike or inflorescence of *Prunella vulgaris* Linnaeus.

**2.1. Botanical**

**2.1.1. Botanical name**

*Prunella vulgaris* Linnaeus of Lamiaceae (mint family).

**2.1.2. Common names**

The plant is called Selfheal, Heal-all or prunella in English and Xiakucao 夏枯草 in Chinese. The fruitspike or inflorescence used in Chinese medicine is known as Xiakucao or more specifically in pharmaceutical name as Spica Prunellae (Anonymous, 1995).

**2.1.3. Botanical description of the plant**

Perennial herb. Stem 4-angled, 20–30 cm high, purple-red, sparsely strigose or subglabrous. Leaves opposite; the petiole 0.7–2.5 cm long, upper ones shorter, the blades lanceolate to oval. Spikes 2–4 cm long, sessile; calyx campanulate, 1 cm long, sparsely hispid, 2-lipped; corolla purplish or white, 1.3 cm long, two-lipped; stamens 4; ovary superior, 2-clefted. Fruits 4-nutlets. Flowering in April–June, fruiting in July–October (Li & Hedge, 1994).

**2.1.4. Description of the herb**

The inflorescence collected are processed by sun-drying method. It is cylindrical in shape, flattened, 1.5–4 cm long, light brown or brownish red, bearing several to 10 or more verticillaster groups of flowers (Hsu et al, 1986).

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**C. Condition of Use :**

### Current use of ingredient

A drink prepared with this herb is available in many herb-tea shops in Hong Kong for frequent patronage. The tea is also available as canned soft drinks in southern China. It is also commonly used as a medicinal herb with the normal dosage of 9-15 g (Anonymous 1995). The Vita Herbal Tea Drink in a 250 mL tetrapack is prepared with less than 2 g per litre of this herb as a flavoring agent. The drink is expected to be consumed mainly by Chinese Americans in North America (U.S. and Canada) China Towns.

#### D. Basis for the GRAS determination

The GRAS determination is experience based on common use in foods.

### E. Availability of information

The search for scientific publications on this safety assessment of this herb and on herbal teas was conducted on the following computer databases:

- (a) Medline of the US National Library of Medicine,
- (b) TCM Database of the Chinese Medicinal Material Research Centre, the Chinese University of Hong Kong,
- (c) CHIMERA, a database on cases of adverse reactions due to Chinese medicines developed by the Chinese Medicinal Material Research Centre, the Chinese University of Hong Kong,

The data and information that are the basis for the determination are available for review and copying by FDA and will be sent to FDA upon request.

### F. Sign and Date

Based on the review of generally available data and the expert consultation provided by Prof. Paul But from the Chinese Medicinal Material Research Centre, the Chinese University of Hong Kong, I believe the use of Selfheal in the Vita Herbal Tea Drink is safe for human consumption; and therefore is exempted from pre-market approval.

Notifier: \_\_\_\_\_

(Mr. Joe Ho, Technical Director of Vitasoy International Holdings Ltd.)

Date : 4 November 1998

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## II. SUMMARY OF IDENTIFICATION AND SPECIFICATION

### 1. Phytochemistry

The herb contains oleanolic acid, ursolic acid, rutin, hyperoside, caffeic acid, vitamins B<sub>1</sub>, C, and K, tannin, essential oil, alkaloid, resin, and 3.5% water-soluble inorganic salts (containing 68% potassium chloride). The spike contains delphinidin, cyanidin, *d*-camphor, ursolic acid, *d*-fenchone, and prunellin (Chang and But, 1987). From the leaves and stems was isolated spinasterol, stigmast-7-enol, methyl ursolate, methyl oleanolate, methyl 2 $\alpha$ ,3 $\alpha$ -dihydroxyursan-12-en-28-oate, methyl 3-epimaslinate, methyl 2 $\alpha$ -hydroxyursolate, methyl maslinate, methyl 2 $\alpha$ ,3 $\alpha$ ,23-trihydroxyolean-12-en-28-oate, and 2 $\alpha$ ,3 $\alpha$ ,24-trihydroxyolean-12-en-28-oic acid (Kojima & Ogura, 1986). Essential oil from the herb contains  $\alpha$ -thujene,  $\alpha$ -pinene, camphene,  $\beta$ -pinene, myrcene, phellandrene, 1,8-cineole, linalool oxide, linalool, 1-nonen-4-ol, menthone, iso-menthone, *p*-menthen-8-ol, terpine-4-ol,  $\alpha$ -citral, piperitone, iso-bornyl acetate, *p*-menthen-8-yl acetate, linalyl acetate, geranyl acetate, decyl acetate,  $\alpha$ -copaene,  $\delta$ -elemene (Zhu et al., 1993).

For the details:

#### *Oleanolic Acid*

*Chemical name:* 3-Hydroxyolean-12-en-28-oic acid

*CAS:* [508-02-1]

*Molecular formula:* C<sub>30</sub>H<sub>48</sub>O<sub>3</sub>

#### *Ursolic acid*

*Chemical name:* 3 $\beta$ -Hydroxyurs-12-en-28-oic acid

*CAS:* [77-52-1]

*Molecular formula:* C<sub>30</sub>H<sub>48</sub>O<sub>3</sub>

*Others:* (i) in the protective wax-like coating of apples, pears, prunes, and other fruits.  
(ii) use: as emulsifying agent in pharmaceuticals and foods.

#### *Rutin*

*Chemical name:* 3-[[6-O-(6-Deoxy- $\alpha$ -L-mannopyranosyl)- $\beta$ -D-glucopyranosyl]oxy]-2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4H-1-benzopyran-4-one

*CAS:* [153-18-4]

*Molecular formula:* C<sub>27</sub>H<sub>30</sub>O<sub>16</sub>

*Others:* (i) found in many plants, especially the buckwheat plant.  
(ii) LD<sub>50</sub> in mice: 950 mg/kg i.v. (propylene glycol soln) (Budavari et al., 1996)  
(ii) therap cat.: capillary protectant.

#### *Hyperoside*

*Chemical name:* 4H-1-Benzopyran-4-one, 2-(3,4-dihydroxyphenyl)-3-( $\beta$ -D-galactopyranosyloxy)-5,7-dihydroxy-

*CAS:* [482-36-0]

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**Caffeic acid**

*Chemical name:* 3-(3,4-Dihydroxyphenyl)-2-propenoic-acid

*CAS:* [331-39-5]

*Molecular formula:*  $C_9H_8O_4$

**Vitamins B<sub>1</sub>**

*Chemical name:* Thiazolium, 3-[(4-amino-2-methyl-5-pyrimidinyl)methyl]-5-(2-hydroxyethyl)-4-methyl-chloride

*CAS:* [59-43-8]

**Vitamins C**

*Chemical name:* Ascorbic acid

*CAS:* [50-81-7]

**Tannin**

*Chemical name:* Tannic acid, gallotannin, corilagin

*Molecular formula:* corilagin :  $C_{27}H_{22}O_{18}$  commercial tannic acid :  $C_{76}H_{52}O_{46}$

*Others:* (i) the chemistry of the tannins is most complex and non-uniform.

(ii) toxicity study: LD<sub>100</sub> in mice : 6.0 g/kg i.g. (Robinson, Graessle, 1943).

(iii) use: mordant in dyeing, manuf. Ink, clarifying beer or wine, etc.

(iv) therap. cat: astringent.

**Delphinidin**

*Chemical name:* 3,5,7-Trihydroxy-2-(3,4,5-trihydroxyphenyl)-1-benzopyrylium chloride

*CAS:* [528-53-0]

*Molecular formula:*  $C_{15}H_{11}ClO_7$

**Cyanidin = Cyanidin chloride**

*Chemical name:* 2-(3,4-Dihydroxyphenyl)-3,5,7-trihydroxy-1-benzopyrylium chloride

*CAS:* [528-58-5]

*Molecular formula:*  $C_{15}H_{11}ClO_6$

**d-Camphor**

*Chemical name:* 1,7,7-Trimethylbicyclo[2.2.1]heptan-2-one

*CAS:* [76-22-2]

*Molecular formula:*  $C_{10}H_{16}O$

*Others:* (i) toxicity data: LD<sub>50</sub> i.p. in mice: 3000 mg/kg (Smith & Margolis, 1954)

(ii) therap cat.: topical anti-infective; topical antipruritic.

**Ursolic acid**

*Chemical name:* 3 $\beta$ -Hydroxyurs-12-en-28-oic acid

*CAS:* [77-52-1]

*Molecular formula:*  $C_{30}H_{48}O_3$

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***d-Fenchone***

*Chemical name:* (1 S)1,3,3-Trimethylbicyclo[2.2.1]-heptan-2-one

*CAS:* [4695-62-9]

*Molecular formula:* C<sub>10</sub>H<sub>16</sub>O

*Others:* (i) use: as flavor in foods; in perfumes.  
(ii) therap. cat.: counterirritant

***α-Spinasterol***

*Chemical name:* (3β, 5α, 22E) Stigmasta-7,22-dien-3-ol

*CAS:* [481-18-5]

*Molecular formula:* C<sub>29</sub>H<sub>48</sub>O

***α-Thujene***

*Chemical name:* (-)-Bicyclo[3,1,0]hex-2-ene, 2-methyl-5-(1-methylethyl)-, (1R)

*CAS:* [3917-48-4]

***α-Pinene***

*Chemical name:* 2,6,6-Trimethylbicyclo[3.1.1]hept-2-ene

*CAS:* [80-56-8]

*Molecular formula:* C<sub>10</sub>H<sub>16</sub>

*Others:* (i) constituent of many volatile oils  
(ii) obtained from oil of turpentine which contains 58-65% α-pinene along with 30% β-pinene.  
(iii) use: manufacture of camphor insecticides, solvents, plasticizers, perfume bases, synthetic pine oil.

***β-Pinene***

*Chemical name:* 6,6-Dimethyl-2-methylenebicyclo-[3.1.1]heptane

*CAS:* [127-91-3]

*Molecular formula:* C<sub>10</sub>H<sub>16</sub>

***Camphene***

*Chemical name:* 2,2-Dimethyl-3-methylenebicyclo-[2,2,1]heptane

*CAS:* [79-92-5]

*Molecular formula:* C<sub>10</sub>H<sub>16</sub>

***β-Myrcene***

*Chemical name:* 7-Methyl-3-methylene-1,6-octadiene

*CAS:* [123-35-3]

*Molecular formula:* C<sub>10</sub>H<sub>16</sub>

*Others:* (i) found in oil of bay, verbena, hop, and others. As an intermediate in the manuf. of perfume chemicals.

***Phellandrene******α-Phellandrene***

*Chemical name:* 2-Methyl-5-(1-methylethyl)-1,3-cyclohexadiene

*CAS:* [4221-98-1]

*Molecular formula:* C<sub>10</sub>H<sub>16</sub>

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- Others:*
- (i) caution: can be irritating to, and absorbed through, skin. ingestion can cause vomiting and diarrhea.
  - (ii) use: in fragrances.

***β-Phellandrene***

*Chemical name:* 3-Methylene-6-(1-methylethyl)cyclohexene  
*CAS:* [555-10-2]  
*Molecular formula:* C<sub>10</sub>H<sub>16</sub>

***Linalool***

*Chemical name:* 3,7-Dimethyl-1,6-octadien-3-ol  
*CAS:* [78-70-6]  
*Molecular formula:* C<sub>10</sub>H<sub>18</sub>O  
*Others:*

- (i) chief constituent of linaloe oil.
- (ii) used in perfumery instead of bergamot or french lavender oil since it has an odor similar to these oils.

***L-Menthone***

*Chemical name:* (-)-5-Methyl-2-(1-methylethyl)-cyclohexanone  
*CAS:* [89-80-5]  
*Molecular formula:* C<sub>10</sub>H<sub>18</sub>O  
*Others:*

- (i) used in perfume and flavor compositions.
- (ii) of the four optically active isomers of menthone, the one occurring most frequently in nature. It is found in various volatile oils.

***p-Menthen-8-ol***

*Chemical name:* Cyclohexenemethanol, α.,α,4-trimethyl-  
*CAS:* [58409-60-2]

***Terpine-4-ol*** = 4-Terpineol

*Chemical name:* 3-Cyclohexen-1-ol, 4-methyl-1-(1-methylethyl)-  
*CAS:* [562-74-3]

***α-Citral***

*Chemical name:* 3,7-Dimethyl-2,6-octadienal  
*CAS:* [5392-40-5]  
*Molecular formula:* C<sub>10</sub>H<sub>16</sub>O  
*Others:*

- (i) citral from natural sources is a mixture of two geometric isomers geranial and neral.
- (ii) use : in synthesis of vitamin A, ionone and methyl-ionone.
- (iii) as a flavor, for fortifying lemon oil, etc.

***Piperitone***

*Chemical name:* 3-Methyl-6-(1-methylethyl)-2-cyclohexen-1-one  
*CAS:* [89-81-6]  
*Molecular formula:* C<sub>10</sub>H<sub>16</sub>O  
*Others:* use: in masking odors in dentifrices.

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***Linalyl acetate***

*Chemical name:* 3,7-Dimethyl-1,6-octadien-3-yl acetate:

*CAS:* [115-95-7]

*Molecular formula:* C<sub>12</sub>H<sub>20</sub>O<sub>2</sub>

*Others:* use: in perfumery

***Copaene***

*Chemical name:* [1R-(1 $\alpha$ , 2 $\alpha$ , 6 $\alpha$ , 7 $\alpha$ , 8 $\alpha$ )]-1,3-Dimethyl-8-(1-methylethyl)tricyclo-[4.4.0.0<sup>2,7</sup>]dec-3-ene

*CAS:* [3856-25-5]

*Molecular formula:* C<sub>15</sub>H<sub>24</sub>

***Cyclohexane***

*Chemical name:* Hexahydrobenzene

*CAS:* [110-82-7]

*Molecular formula:* C<sub>6</sub>H<sub>12</sub>

*Others:* (i) use: solvent for lacquers and resins, in fungicidal formulations (possesses slight fungicidal action).  
(ii) caution: high concentration may act as narcotic, skin irritant (Browning, 1965)

 ***$\alpha$ -cyclohexane***

*Chemical name:* 6-Ethenyl-6-methyl-1-(1-methylethyl)-3-(1-methylethylidene)-, (S)-

*CAS:* [5951-67-7]

**2. Method of Manufacture**

In Asian countries, Selfheal is processed by drying.

**3. Pharmacology**

Methanol extracts of the herb showed significant (ED<sub>50</sub> < 20  $\mu$ g/ml) cytotoxicity in the KB and P-388 tissue culture cells. Ursolic acid was identified as one of the cytotoxic principles (Lee et al., 1988). Water extract of the herb showed diuretic effect (Haginiwa & Harada, 1963). Extracts of the herb also showed antiviral (Kurokawa et al. 1993), antioxidant (Lamaison et al., 1991), anti-HIV (Chang & Smith, 1989; Yao et al., 1992; Yamasaki et al., 1993.), and antimutagenic effects (Lee & Lin, 1988; Horikawa et al., 1994).

**4. Specification for food-grade material**

The herb remains clean and not contaminated.

**III. SUMMARY OF SELF LIMITING LEVELS OF USE**

If Selfheal is added to food above its self-limiting level, the food becomes unappealing and has medicinal purpose for general consumption.

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#### **IV. COMMON USE GRAS DETERMINATION**

##### **1. Technical evidence of safety**

###### **1.1. History of use (Folk medicinal uses)**

This herb has been used in Chinese medicine for over 2,000 years. It alone or mixed with other herbs has been used as a general tonic (Hu, 1997).

It is regarded in Chinese medicine as bitter with a pungent flavor and a "cold" property. It enters the channels of liver and gallbladder meridians. It is reputedly good for dispersing liver heat and dissolving accumulations. It is commonly prescribed in goiter, scrofula, conjunctivitis, carbuncle, photophobia, pinkish leukorrhea, edema, nephritis, headache and dizziness, mastitis with swelling and pain, hyperplasia of breast, hypertension, hepatitis, tuberculosis and mammary cancer. Normal dosage: 15–30 g (Chang and But, 1987; Kimura, 1996).

###### **1.2. Toxicity assessment**

###### **1.2.1. Acute toxicity**

In ICR mice,  $LD_{50} > 50$  g/kg p.o. (Yang & Chen, 1997).

In human, occasional hypersensitivity (mainly rashes) (Han, 1983; Tian, 1983; Xia, 1992).

###### **1.2.2. Chronic toxicity**

Subchronic toxicity tests in rats given 5–10 g of the herb/kg p.o. showed an increase in urinary protein, BUN and heart wet weight, but decrease in SGPT (Yang & Chen, 1997).

##### **2. Safety assessment**

According to the American Herbal Products Association's *Botanical Safety Handbook* (McGuffin et al., 1997), Selfheal is classified as Class 1 which is defined as herbs that can be safely consumed when used appropriately.

The herb has been used for over 2,000 years in Chinese medicine, and is commonly prescribed in treating 'hot' syndromes in Chinese medicine and used in making herbal teas (Hu, 1997). Rarely, individual patients may be allergic to this herb if taken in rather large quantities.

The diluted concentrations in the proposed the Vita Herbal Tea Drink to be manufactured by Vitasoy International Holdings Ltd. is not expected to cause serious side effects.

## References:

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## I. GRAS EXEMPTION CLAIM

9

### A. Name and Address of Notifier :

Mr. Joe Ho (Technical Director)  
Vitasoy International Holdings Ltd., 1, Kin Wong Street, Tuen Mun, New Territories, Hong Kong.

### B. Name of Substance :

1. **Sophora flower bud** is commonly known as Huaimi 槐米 in Chinese.

#### 2. **Description**

The source of this herb is the immature flower bud of *Sophora japonica* Linnaeus. It is known as Huaimi 槐米 or Huaihuami 槐花米 in Chinese.

#### 2.1. **Botanical**

##### 2.1.1. **Botanical name**

*Sophora japonica* L. is a member of Fabaceae (pea family).

##### 2.1.2. **Common names**

The plant is called Pagoda tree in English and Huaishu 槐樹 in Chinese. The immature flower bud used in Chinese medicine is commonly known as Huaimi 槐米 or Huaihuami 槐花米, while the blossomed flowers are known as Huaihua 槐花; both are collectively and specifically known in pharmaceutical name as Flos Sophorae (Anonymous, 1995).

##### 2.1.3. **Botanical description of the plant**

Deciduous trees, growing to 25 m. The bark is dark gray in color and shallowly cracked, with inner side yellow in color, with an unpleasant odor; branches brown in color, young in green color, with hair and prominently marked with lenticels. Leaves are alternate, 25 cm long, base of leaf stalk swollen, The individual leaflets are oval in shape, 2.5-5 cm long, 1.5-2.6 cm wide, pointed apex and round base; green and shiny in the upper surface of leaf; lower surface covered with short, white hair. Leaflet stalk, 2.5 cm long.

##### 2.1.4. **Description of the herb**

The flower buds oval or elliptical shaped, 2 -6 mm long, 2 m in diameter. Longitudinal stripes on the lower part of sepals. The petals remain unopened and are yellowish white. Light weight, fragile (Anonymous, 1995). Based on the content of rutin, commodities with a yellowish green color are considered better quality (Zhang & Wang, 1993).

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### C. Condition of Use :

### Current use of ingredient

Sophora flower bud is an ingredient in the Five Flower Tea, and also commonly used in preparing herbal teas in Hong Kong and southern China (Hu, 1997). It is also used as a medicinal herb with the dosage of 5-9 g (Anonymous 1995).

The Vita Herbal Tea Drink in a 250 mL tetrapack is prepared with less than 2.5 g per litre of this herb as a flavoring agent. The drink is expected to be consumed mainly by Chinese Americans in North America (U.S. and Canada) China Towns.

#### D. Basis for the GRAS determination

The GRAS determination is experience based on common use in foods.

### E. Availability of information

The search for scientific publications on this safety assessment of this herb and on herbal teas was conducted on the following computer databases:

- (a) Medline of the US National Library of Medicine,
- (b) TCM Database of the Chinese Medicinal Material Research Centre, the Chinese University of Hong Kong,
- (c) CHIMERA, a database on cases of adverse reactions due to Chinese medicines developed by the Chinese Medicinal Material Research Centre, the Chinese University of Hong Kong,

The data and information that are the basis for the determination are available for review and copying by FDA and will be sent to FDA upon request.

### F. Sign and Date

Based on the review of generally available data and the expert consultation provided by Prof. Paul But from the Chinese Medicinal Material Research Centre, the Chinese University of Hong Kong, I believe the use of Sophora flower bud in the Vita Herbal Tea Drink is safe for human consumption; and therefore is exempted from pre-market approval.

Notifier .

(Mr. Joe Ho, Technical Director of Vitasoy International Holdings Ltd.)

Date : 4 November, 1998.

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## II. SUMMARY OF IDENTIFICATION AND SPECIFICATION

### 1. Phytochemistry

Rutin 10-25%; Flavonoids: kaempferol sophoroside, genistein, quercetrin;  
Triterpenoids: betulin, sophoradiol; sophorin A, B, C. (Hsu *et al.*, 1986)

For the details:

#### **Rutin**

**Chemical name:** 3-[[6-O-(6-Deoxy- $\alpha$ -L-mannopyranosyl)- $\beta$ -D-glucopyranosyl]oxy]-2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4H-1-benzopyran-4-one

**CAS:** [153-18-4]

**Molecular formula:**  $C_{27}H_{30}O_{16}$

**Others:** (i) found in many plants, especially the buckwheat plant.  
(ii) LD<sub>50</sub> in mice: 950 mg/kg i.v. (propylene glycol soln).  
(Budavari *et al.*, 1996)  
(ii) therap cat.: capillary protectant.

#### **Kaempferol**

**Chemical name:** 3,5,7-Trihydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran-4-one

**CAS:** [520-18-3]

**Molecular formula:**  $C_{15}H_{10}O_6$

**Others:** it is a plant flavonoid.

#### **Genistein**

**Chemical name:** 5,7-Dihydroxy-3-(4-hydroxyphenyl)-4H-1-benzopyran-4-one

**CAS:** [446-72-0]

**Molecular formula:**  $C_{15}H_{10}O_5$

**Others:** (i) phytoestrogen found in soy product; the aglucon of genistin and of sophoricoside.  
(ii) use: chemical probe to explore signal transduction pathways.

#### **Betulin**

**Chemical name:** Lup-20(29)-ene-3,28-diol, (3 $\beta$ )-

**CAS:** [473-98-3]

**Molecular formula:**  $C_{30}H_{50}O_2$

#### **Sophoradiol**

**Chemical name:** Olean-12-ene-3,22-diol, (3 $\beta$ ,22 $\beta$ )-

**CAS:** [6822-47-5]

### 2. Method of Manufacture

In Asian countries, Sophora flower bud is processed by drying.

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### **3. Pharmacology**

Scientific studies on the flower buds have shown antifungal and hypotensive effects. Radioprotective effect has been reported (Sokol'chik et al., 1992).

### **4. Specification for food-grade material**

The herb remains clean and not contaminated.

## **III. SUMMARY OF SELF LIMITING LEVELS OF USE**

If Sophora flower bud is added to food above its self-limiting level, the food becomes unappealing and has medicinal purpose for general consumption.

## **IV. COMMON USE GRAS DETERMINATION**

### **1. Technical evidence of safety**

#### **1.1. History of use (Folk medicinal uses)**

It has a bitter flavor and a mild cold property. It enters the channels of the liver and the large intestine meridians. It is reputedly good for removing heat, cooling blood, controlling bleeding, strengthening heart and blood vessels. It is most commonly prescribed in hematemesis, epistaxis, hematochezia, hemorrhoids, hematuria, hemorrhinia, conjunctivitis, leukorrhea, uterine or intestinal hemorrhage, phyodermas, metrorrhagia, arteriosclerosis, and hypertension.

Contraindications: spleen and stomach deficiency.

Side effects: Anaphylactic response causing rashes.

Normal dosage: 6-15 g (Hsu et al., 1986)

#### **1.2. Toxicity assessment**

##### **1.2.1. Acute toxicity**

No reference is available. There is a report of allergy in a 5-year-old girl who placed Sophora flowers in her mouth (Ma, 1964); the exact condition or amounts involved were not given in the article.

##### **1.2.2. Chronic toxicity**

No reference is available.

### **2. Safety assessment**

Sophora flower bud is commonly used in preparing herbal teas in Hong Kong and southern China (Hu, 1997). The low concentration of this herb extract in the Vita

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Herbal Tea Drink to be manufactured by Vitasoy International Holdings Ltd. is not expected to cause any adverse reaction upon normal consumption.

**References:**

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TRANSMISSION END

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Pages 000065 – 000066 not included.

GRN 000013

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Soymilk, Beverages, Tofu, Oriental Pasta, and Specialty Items

March 3, 1999

Dr. Lawrence J. Lin, Ph.D.  
Office of Pre-Market Approval Department  
FOOD & DRUG ADMINISTRATION  
200 C Street SW, HFS - 206  
Washington DC 20204

Dear Dr. Lin:

**RE: HERBAL TEA DRINK - SAFETY ASSESSMENT REFERENCES**

As you have requested, enclosed are the references for the "Safety Assessment of Nine Herbal Ingredients." If you need additional documentation, please do not hesitate to contact me at (415) 285-1130 x203 or fax (415) 285-0327.

Thank you!

Sincerely Yours,

Janet M. Pang  
R&D Manager

Enclosure

cc: (Letter only) Sue Lau - Product Development Manager, Vitasoy Int'l Holdings Ltd.

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Vitasoy (U.S.A.) Inc. HDQ • 400 Oyster Point Blvd. Suite 201, South San Francisco, CA 94080 Phone (415) 583-9888 (800) VITASOY Fax (415) 583-8881

Manufacturing • 1575 Burke Avenue, San Francisco, CA 94124 Phone (415) 285-1130 Fax (415) 285-0327

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Soymilk, Beverages, Tofu, Oriental Pasta, and Specialty Items

July 9, 1999

Mr. Alan M. Rulis, PhD  
Director  
Office of Pre-market Approval  
Center for Food Safety and Applied Nutrition  
Food and Drug Administration  
200 C Street SW  
Washington DC 20204

Dear Mr. Rulis,

Ms. Janet Pang has received your letter about proving six more herbs to be GRAS. And the herbs are as followed:

Lonicera Japonica (honeysuckle)  
Lophatherum Gracile  
Morus Alba (mulberry leave)  
Plumeria Rubra  
Prunella Vulgaris (self-heal)  
Sophora Japonica (pagoda tree blossom)

We are going to do that as well and as fast as we can. However, could you please give us more direction in what kind of information the FDA is looking for? The information will help Vitasoy by avoiding us from getting information in a wrong direction and something FDA does not need. Attached is my business card for contacting purposes. Could you kindly send me your business card also. Thank you for your attention and I am looking forward to hearing from you soon.

Sincerely,

Rosanne Au-Yeung  
Food Technologist  
Research and Development Dept.

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1575 Burke Avenue, San Francisco, CA 94124

## *Reference List for Industry Submission, GRN 000013*

<i>Pages</i>	<i>Author</i>	<i>Title</i>	<i>Publish Date</i>	<i>Publisher</i>	<i>BIB_Info</i>
000068 - 000099	Hu, Shiu Ying	Herbal Teas and Populace Health Care in Tropical China	1997	American Journal of Chinese Medicine	Volume XXV, Number 1, pgs 103-134
000100 - 000105	NA	Flos Lonicerae	1992	Pharmacopoeia of the Peoples Republic of China	NA
000106 - 000109	NA	Herba Lophatheri	1995	Pharmacopoeia of the Peoples Republic of China	NA
000110 - 000113	NA	Spica Prunellae	1995	Pharmacopoeia of the Peoples Republic of China	NA
000114 - 000117	NA	FLOS Sophorae	NA	Pharmacopoeia of the Peoples Republic of China	NA

*NA- Not applicable*